THE CANADIAN MEDICAL ASSOCIATION

LE JOURNAL DE

L'ASSOCIATION MÉDICALE CANADIENNE

MAY 27, 1961 • VOL. 84, NO. 21

AUTOIMMUNIZATION – A POSSIBLE MECHANISM OF TISSUE INJURY* I–THEORETICAL AND EXPERIMENTAL ASPECTS†

JAN W. STEINER, M.D. and
ROBERT VOLPE, M.D., F.R.C.P.[C],
Toronto

IMMUNITY in its broadest sense was conceived as a defensive reaction of the organism. The term autoimmunity may be used to refer to a state of self-protection, and autoimmune reactions to processes concerned with defence against self-intoxication. The term, however, has come to be applied to processes with the very opposite meaning, namely, to reactions of self-destruction.

Immunologic reactions can be either beneficial or harmful to the host. Yet fundamentally they are the result of an identical response of the organism, or of its antibody-producing apparatus, to contact with an antigen. We may draw a distinction between physiologic and pathologic immune reactions to facilitate our understanding of these processes; we must, however, insist that no sharp dividing lines exist between them and that a particular twist, an exaggerated reaction or some special circumstance, may convert a harmless process into a pathologic one.

These considerations must be borne in mind when discussing the problems of autoimmunity, since the significance of physiologic and pathologic autoimmune processes and their relationship to each other have as yet not been fully elucidated.

It is the purpose of this paper to analyze the present theoretical, experimental and clinical knowledge of the processes of autoimmunization. An attempt will be made to eliminate the beneficial and identify the possible harmful effects of autoimmune reactions and to integrate these into the accepted scheme of mechanisms of immunologic tissue injury.

*From the Departments of Pathology and Medicine, University of Toronto, Toronto.
Parts of the investigations referred to in this review were supported by grants-in-aid from the National Research Council of Canada (MA-785 and MA-859).
†This is the first of three instalments in which this article will be published. The complete bibliography will follow the final instalment.

BASIC CONCEPTS OF AUTOIMMUNITY

The physician's initial interest in endogenous causes of disease, exemplified by the "humours" of the Greeks and "spirits" turned outward after the discovery of biologic pathogens. When the antigenicity of bacteria and even of such apparently harmless substances as blood cells and milk was recognized, the term antigen became synonymous with *foreign* protein. Immunology was developed for the purpose of elucidating the organism's reactions to exogenous pathogens. Endogenous factors as causes of immunologic injury were excluded from the accepted theories of immunology on the basis of Ehrlich's concept of "horror autotoxicus" which suggested that the body avoids making antibodies that might damage its own tissues.[53]

Ehrlich provided a loophole for further thought on the subject by his suggestion that autoantibodies may be produced as a physiologic mechanism by which the body protected itself against autointoxication. Thus, in modern terminology, he rejected autoclastic (self-destroying) processes but admitted the possibility of autoimmune (self-protecting) mechanisms in disease.

ANTIGENICITY OF TISSUE COMPONENTS

The initial steps in the study of autoimmunity were antigen-centred. Proof had to be provided that tissue components, cells and extracellular substances could become antigenic.

Masugi[109] showed that not only were tissue components antigenic in heterologous animals (rabbit-rat system) but that antibodies developing in the recipient possessed a pathogenic potential when re-injected into the donor animal (Figs. 1 and 2). In accordance with classical dogma, antigenicity of heterologous tissue components was understandable since species differences of tissue components were apparently sufficiently marked to allow them to be treated as foreign by the recipient.

As a first step to reconciling classical theory with the phenomenon of autoimmunity, it was suggested that conversion of an autologous tissue component to an antigen may not be necessary. If exogenous antigens, e.g. bacteria, shared some characteristics in common with endogenous substances, or became bound to exogenous structures,[96] then antibodies against the former may be capable of interacting

Canad. M. A. J.
May 27, 1961, vol. 84

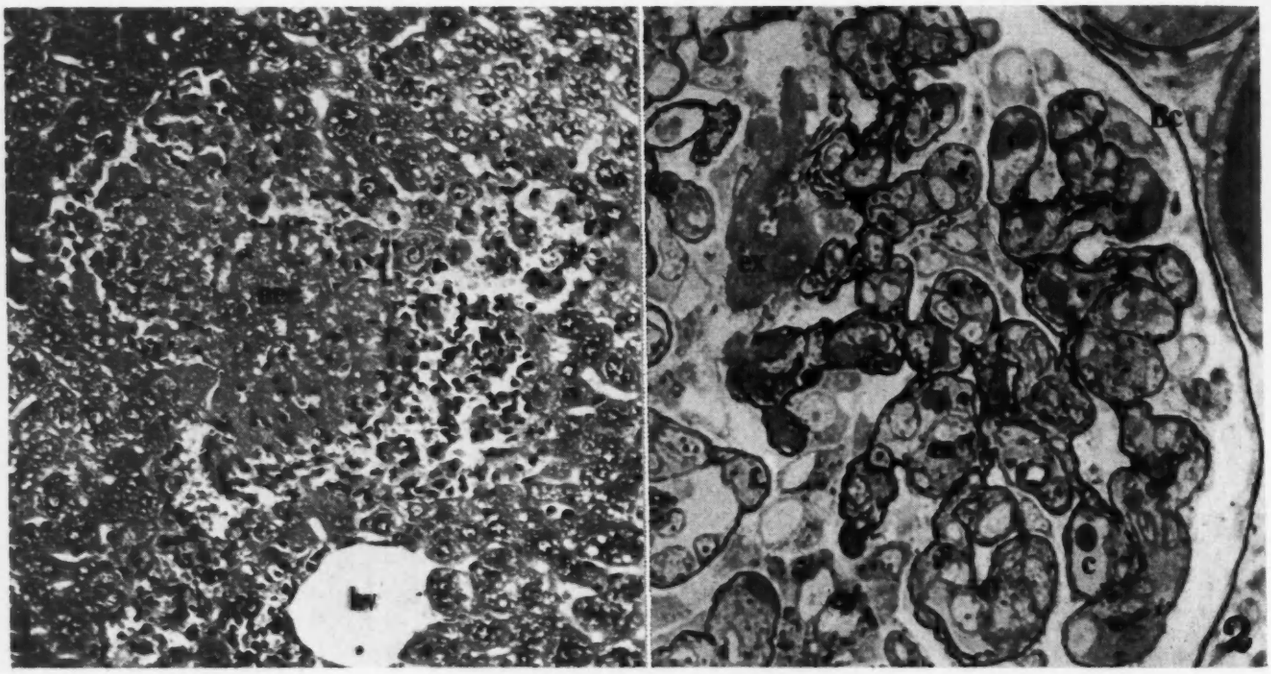


Fig. 1.—An example of a Masugi-type tissue injury by the intravenous injection into a mouse of a rabbit anti-mouse-liver serum. Note that the injury in this instance takes the form of a necrotizing lesion in the midzone of a hepatic lobule. H. and E., × 216. (hv-hepatic vein; nec-necrosis.) Fig. 2. — An example of a Masugi-type tissue injury induced by the intravenous injection into a dog of a rabbit anti-dog-kidney serum. Note that the lesion is predominantly proliferative—endothelial cells almost fill the lumina of capillaries—and exudative. Necrosis is not a feature of this injury. Thin (2 μ) section, periodic acid-silver methenamine, × 720. (c- glomerular capillary lumina; en- endothelium; ep- epithelium; ex-exudate in Bowman's space; Bc- Bowman's capsule.)

with the latter.[68, 69] However, entry of exogenous antigens could not always be demonstrated.

It was already known that exogenous non-antigenic substances could attach themselves to endogenous proteins, and alter them sufficiently to render them antigenic. An example of this is the purpura induced by the administration of apronal (Sedormid).[1] It was conversely suggested that the entry of antigens, e.g. viruses which attached themselves to or entered into cells, may have altered their composition in such a way as to render them foreign and consequently antigenic. Thus tissue components were regarded as endogenous haptens whose antigenicity could be potentiated by fully fledged exogenous antigens.[98] The tissue haptens were thought to be capable of reacting with antibody but unable to stimulate its production until linked to an exogenous protein to which they then imparted their own immunologic specificity.

These thoughts were in accordance with Burnet and Fenner's hypothesis.[16] The normal non-antigenicity of body constituents was visualized as being dependent upon markers on the surfaces of cells which allowed self-recognition by antibody-producing cells. Any injury to cells, biologic, physical or chemical, which altered or destroyed the marker would then convert them from self to not-self and an autoantigen would be created.

The self-marked mechanism evolved during embryogenesis as a result of contact between tissue constituents and the reticuloendothelial (RE) system. It has been shown that the reactivity of the antibody-forming tissues is largely determined by the antigens present when these tissues are reaching maturity, about the time of birth. All those antigens which have access to such tissues induce immunologic tolerance in the individual.[9] Those substances, e.g. thyroglobulin, which had never been in contact with elements of the RE system, required separate consideration. The mere release of such substances from their sheltered locations, e.g. thyroid follicles, would suffice to initiate autoimmunization since they were normally not provided with self-markers. This concept has been recently questioned, since it was found that the administration of thyroglobulin during the immediate postnatal period did not prevent the development of autoantibodies after challenge with thyroglobulin at a later date.[38]

Dameshek[34] propounded the theory that the active endometrium, associated with pools of stagnant blood, may be the ideal medium for the conversion of altered blood cells and blood vessels to autoantigens.

There is at present no conclusive evidence available which would allow us to determine whether autoimmunization is the result of subtle alterations in the chemical constitution of tissue constituents or whether it results from failure to acquire tolerance.

CIRCULATING AUTOANTIBODIES

The theoretical assumptions outlined above stimulated the search for antibodies directed against autologous (i.e. the organism's own) tissue components. As early as 1926 precipitins active against lung extracts were demonstrated in patients suffering from tuberculosis.[95] Their presence was subsequently confirmed by complement-fixing and

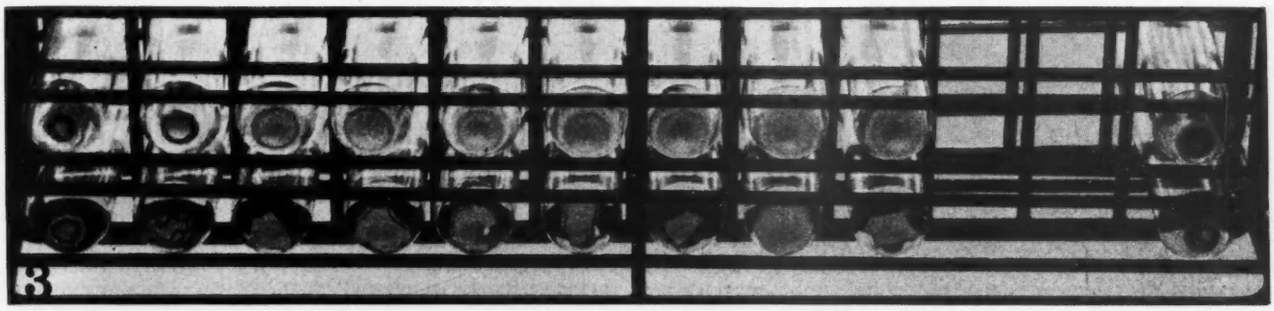


Fig. 3.—Tanned red cell hemagglutination procedure for the demonstration of antithyroglobulin antibodies. The rack containing the test-tubes is viewed from a mirror below. The two separate tubes at the extreme right serve as controls containing tanned but uncoated red cells and the suspected sera. In the remaining tubes in both rows the red cells are coated with thyroglobulin and incubated with serial dilutions of the patient's sera. The upper row shows a negative result with the cells aggregated in a ring at the bottom of the tubes. The lower row is from a patient with Hashimoto's disease. Note that the cells remain spread out and the edges of the carpet of cells fold. This test is positive in all tubes.

flocculation procedures.[6, 55] With the introduction of more sensitive methods of antibody detection, particularly the autoimmune complement fixation test (AICF)[58] and the tanned red cell agglutination procedure (TRCA) (Fig. 3),[12] the list of demonstrable autoantibodies grew. They were identified in rheumatic fever,[25, 171] glomerulonephritis,[93, 99, 171] disseminated lupus erythematosus,[59] in various liver diseases,[10, 51, 59, 104] in macroglobulinemia and paraproteinemia,[104] in disseminated sclerosis[139] and sympathetic ophthalmia.[110, 184] Their numbers increased with the finding of autoantibodies in such diverse conditions as idiopathic male sterility,[179] chronic pancreatic disease,[165] Sjögren's syndrome[80] and idiopathic Addison's disease.[4] Anti-heart antibodies were demonstrated in rheumatic disease[84] as well as in angina pectoris and in myocardial infarction,[62] intrinsic factor antibodies in some cases of pernicious anemia[148] and thyroid antibodies in various thyroid diseases.[143] This by no means exhausts the list of autoantibodies which have been found. The subject has been previously adequately reviewed.[49, 89, 147, 170, 172, 175]

As these investigations progressed, adjustments to existing theories became imperative. It was found that a given patient may have antibodies against several tissue antigens simultaneously. The explanation for such phenomena required the assumption that diverse tissues possess similar or identical components capable of becoming antigenic (i.e. vascular elements), or that tissue antigens share certain common characteristics so that an antibody against one reacts with another or several others. This was amplified by the suggestion that in the process of converting an innocuous tissue component to an antigen, biologic, physical or chemical degradation of the cellular or extracellular constituents may lead to some loss of specialized features which normally distinguish tissues and cells from each other. Thus one degraded tissue constituent may come to resemble another more closely than would be normally the case.

It was also realized that the methods employed for demonstrating autoantibodies revealed differing antigenic affinities. The autoantibodies demonstrable in thyroid disease by the TRCA method were found to be directed against thyroglobulin,[181, 182] whereas those uncovered by the AICF procedure reacted with components (microsomal fractions) of thyroid epithelial cells.[7] Complement-fixing and tanned red cell agglutinating antibodies could be present in the serum of the same patient.[46] Thus it was realized that more than one component of an organ could become antigenic.

Significance of Circulating Autoantibodies

It is axiomatic that an antigen and its specific antibody cannot exist in free form in a given system. Our ability to demonstrate *free*, circulating autoantibodies suggests that the antigens to which they are complementary are not available or not accessible. Grabar[69] suggested an alternative explanation that free autoantibody does not become demonstrable until all antigenic sites have been saturated with antibody.

It is at present not clear whether an antibody formed against an altered tissue antigen can subsequently react with its normal, unaltered counterpart *in vivo*. *In vitro* this possibility exists and has been demonstrated.[60] It stands to reason, however, that autoantibodies to altered liver cells or to glomerular components, for example, should never be demonstrable if one considers the mass of available antigen. Thus antigen saturation followed by antibody overflow may be an acceptable explanation for inaccessible antigens, e.g. thyroglobulin, but is difficult to accept in instances of easily available and readily accessible antigens.

These considerations are important since it was suggested that autoantibodies may provide an explanation for the progression to chronicity of a lesion initiated by viral injury (e.g. viral hepatitis progressing to cirrhosis). If the initiation of autoimmunization by the virus provided the necessary antigen to evoke autoantibody production, then the subsequent course of the disease would be dictated by either recurrent or continued availability or release of the antigen, or the antibody would have to be capable of interacting with intact liver cells. Similar considerations apply to the causation and progression of glomerulonephritis where exogenous streptococcal antigens are thought

Canad. M. A. J.
May 27, 1961, vol. 84

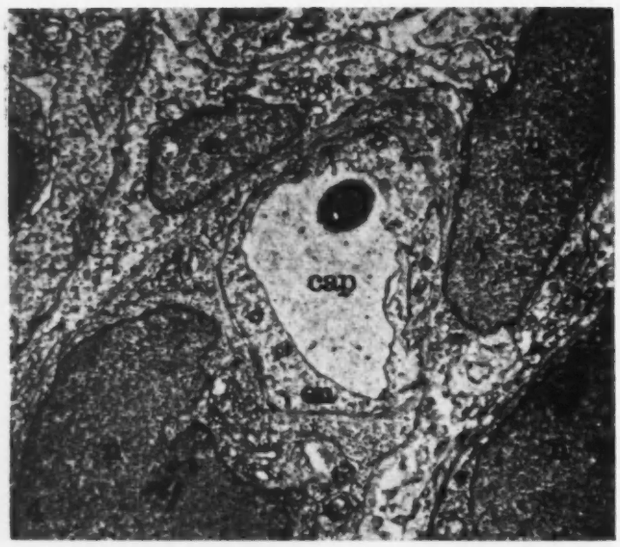


Fig. 4.—Mesenchymal stem cells in the connective tissue of an embryo. Note the large nuclei relative to the amount of cytoplasm. At this stage the future development of such cells cannot be predicted, though they may differentiate in the direction of immunologically competent cells. They represent the primitive undifferentiated mesenchymal component of clones of i.c.c.'s. Electron micrograph. Osmium tetroxide, × 8000. (cap- capillary lumen; en- endothelium; n-nuclei of mesenchymal cells.) (Courtesy of Dr. T. Leeson.)

to be involved at the outset, to be followed by autoimmunization and chronicity.

Such speculations, however, presuppose that circulating autoantibodies are capable of producing tissue injury. Actually, the available evidence points to their lacking such pathogenicity. Passive immunization of a rhesus monkey with large amounts of Hashimoto serum containing a large quantity of antibody, which cross-reacted with monkey thyroid *in vitro*, failed to produce thyroid lesions in the recipient. Using Coon's fluorescent antibody technique, the antibody could not be found localized in the monkey thyroid.[142, 144] A direct cytotoxic effect could not be demonstrated *in vitro* when high-titred Hashimoto sera were added to thyroid cell tissue cultures.[143] Later, Pulvertaft *et al.*[132] were able to demonstrate a cytotoxic agent in the sera of patients with Hashimoto's disease which was active against thyroid cells in tissue culture. This agent was not identical with the antithyroid cell antibody demonstrable by the AICF test and was also different from the tanned red cell agglutinating antithyroglobulin antibody. Further, Clough[28] quotes experiments in which large amounts of sera of patients with rheumatoid arthritis containing anti-gamma-globulin autoantibodies administered to normal volunteers and to subjects with rheumatoid arthritis in a relatively quiescent stage failed to cause any disturbance whatsoever. In experimental autoallergic encephalomyelitis passive transfers of antibody-containing serum fail to produce the disease in normal animals even after intracisternal injections.[75, 81, 82] The amount of circulating antibody does not correlate with the severity of the lesions in experimental animals.[3, 129, 151] Some suspected autoimmune diseases, e.g. systemic lupus erythematosus, occasionally occur in the absence of demonstrable circulating antibodies.[28]

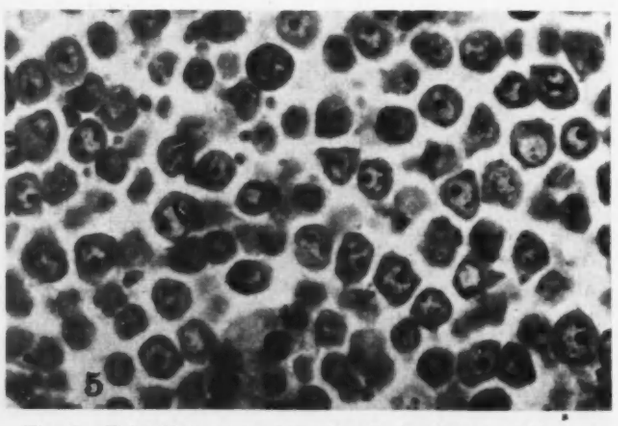


Fig. 5.—Primitive mesenchymal cells in the synovial cavity of a rabbit after an intra-articular injection of foreign protein. These cells (plasmablasts) already show a tendency to differentiate in the direction of immunologically competent cells. They represent the primitive, partly differentiated component of clones of i.c.c.'s. Giemsa stain, × 1100.

In assessing the significance of circulating autoantibodies, the problem of recovery of patients with circulating autoantibodies must also be considered.[146] Recovery from infectious diseases is achieved, amongst other mechanisms, by means of antibodies. How does a patient recover from a disease caused by antibodies? One may speculate that recovery of such cases supports the thesis that autoantibodies are the result rather than the cause of disease.

ANTIBODY-CENTRED THEORIES

We have up to now explored antigen-centred concepts which attempted to explain autoimmunization as primarily a response to antigenic instruction, i.e. an autoantigen was thought to be required before activation of the RE system could occur.

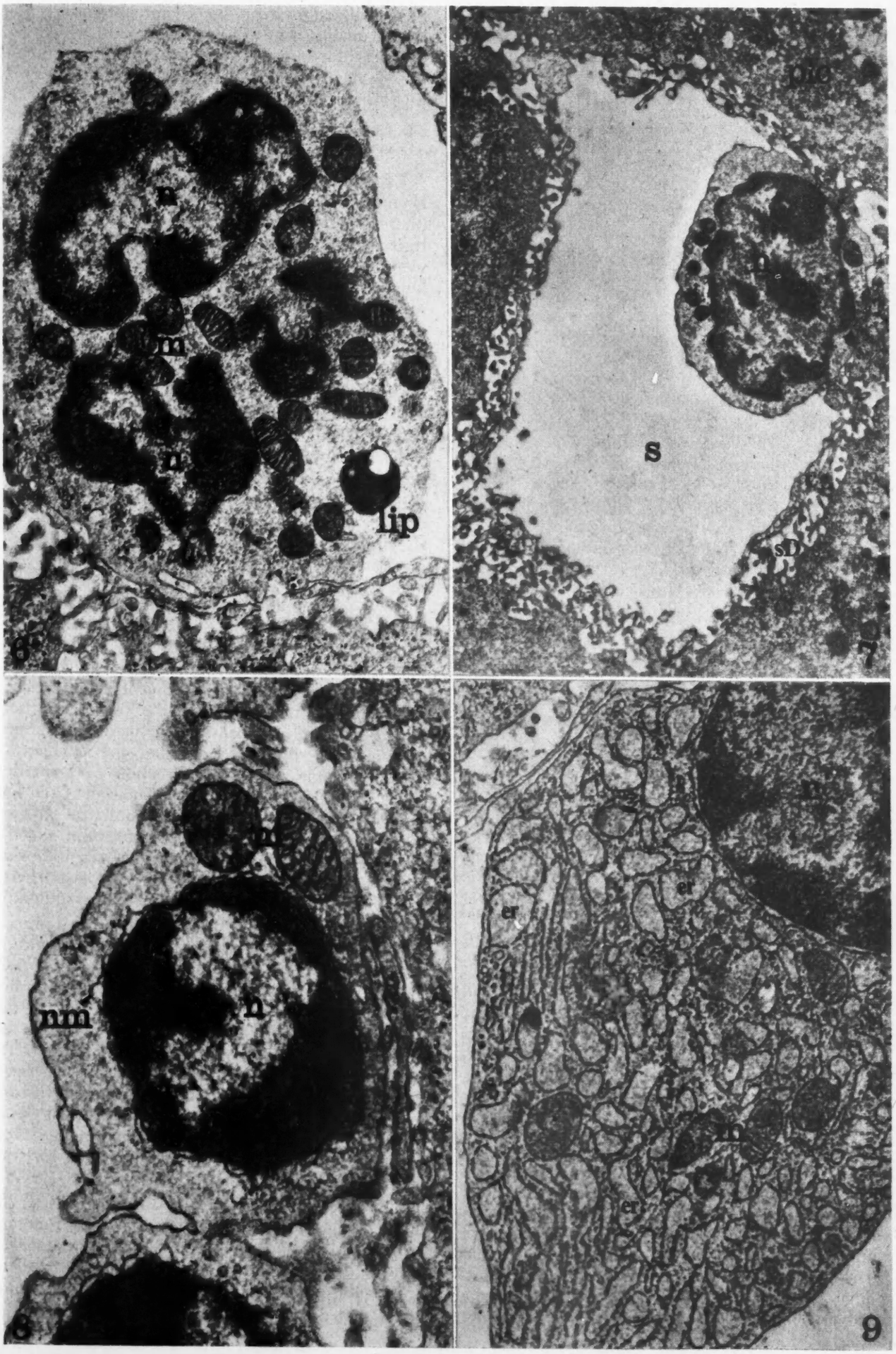
Figs. 6 to 9.—Electron micrographs of mature components of a hypothetical clone of immunologically competent cells. (From the liver of a rabbit hyperimmunized with foreign protein.)

Fig. 6.—A histiocyte with a folded nucleus (sectioned in 3 planes) and numerous mitochondria. A lipid inclusion is present in the cytoplasm. The role of these cells is thought to be phagocytosis of antigens and their gradual release to the remaining cells of the clone. Autodestructive propensities in the experimental autoimmune disorders are attributed to this cell. Osmium tetroxide and protargol, × 20,800.

Fig. 7.—A fixed phagocytic littoral cell (Kupffer cell) forming by virtue of its trabecula the lining of a hepatic sinusoid. Its function within the clone is thought to be similar to that of the mobile histiocyte. Osmium tetroxide and protargol, × 13,200.

Fig. 8.—A lymphocyte with its prominent nucleus and scanty cytoplasm. Its function in the clone may be the storage of "immunologic memory". Osmium tetroxide and protargol, × 30,240.

Fig. 9.—A mature plasma cell showing the distended vesicles of the endoplasmic reticulum within its cytoplasm. The faintly electron-dense material within these is thought to represent gamma globulin. The function of this cell in the clone is thought to be the elaboration of antibody. Osmium tetroxide and protargol, × 21,600.
(n- nucleus; m- mitochondria; nm- nuclear membrane; er- endoplasmic reticulum; S- liver sinusoid; t- trabecula of Kupffer cell; sD- space of Disse; pic- parenchymal liver cell; lip- lipid inclusion.)


n
m
lip
6
S
sD
7
nm
n
8
er
er
er
9

Burnet has provided a totally new approach to the study of autoimmunization by his Clonal Selection Theory of Acquired Immunity.[16-23] This concept is antibody-centred.

A clone is a population derived from asexual replication of a unit, whether an organism or cell; and whenever a new inheritable character appears by mutation or any other means, a new clone is said to be initiated. Mesenchymal cells are divided into populations (clones) composed of immunologically competent cells (i.c.c.) which are competent towards a certain antigenic determinant, i.e. they are capable of responding to contact with an antigen, to which they are attuned, either by production of a specific antibody or by some other specialized behaviour. Such a hypothetical cell population is depicted in the light and electron micrographs (Figs. 4 to 9). The specific capacity of cells to react immunologically, either as a producer of antibody or as a cell, is conferred on it genetically. If the relevant antigenic determinant makes contact with a member of an appropriately attuned clone, activation of the pre-existent system results. Prenatal selection (elimination of undesirable clones) leaves the organism without clones capable of reacting with endogenous antigens or potential antigens. The undesirable patterns have supposedly been eliminated "in one way or another".[23]

Burnet suggests that the population dynamics of mesenchymal cells allow for a high degree of postnatal regenerative activity with a considerable chance of somatic mutation. Mutant, "forbidden" clones lacking the capacity of recognizing self may arise in the course of a lifetime which may then be capable of acting pathogenically either as cells or as antibody producers.

The chances of adverse mutations are high, yet the incidence of suspected autodestructive disorders is low. This implies that a homeostatic mechanism must exist. It is suggested that during the process of proliferation of an activated i.c.c. it may go through stages in which further contact with antigen will result in its inhibition or destruction. This is supported by the phenomenon of immunologic paralysis which can be induced in an animal by oversaturation with a soluble antigen.[44] Such an animal is unable to produce antibody against the corresponding antigen for a limited period of time.[150] Despite postulated frequent mutations of cells to new and forbidden immunologic patterns, they do not produce antibody against accessible body components in the normal individual because of the existence of immunologic homeostasis.

Thus the clonal selection approach to the study of autoimmunization has evolved a concept of autodestructive diseases as primary disorders of immunologically competent cells of the mesenchyme. They may be caused by survival of forbidden mutants of reticuloendothelial cells as a result of a breakdown of homeostatic mechanisms. Such cells or their products (autoantibodies) may then damage tissue. The antigens with which they interact play merely a passive role by attracting the damaging elements (cells or antibodies) to those organs in which the antigen resides.

EXPERIMENTAL EVIDENCE OF AUTOIMMUNITY

Experimental autodestructive disorders have been produced in brain,[81-83, 87] spinal cord and peripheral nerves,[174] kidney,[79] lens[120] and uveal tract,[29a] testis,[56] thyroid[181] and adrenal.[156] They were to serve as experimental counterparts of such human diseases as postinfectious encephalomyelitis, multiple sclerosis, Guillain-Barré polyneuritis, glomerulonephritis, phaco-anaphylactic endophthalmitis, postinfectious iridocyclitis, sympathetic ophthalmia, mumps orchitis, non-endocrine chronic infertility, mumps thyroiditis, Hashimoto's disease and idiopathic Addison's disease (cytotoxic adrenal contraction).

All the experimental prototypes were produced by injections of the animal's own tissue homogenates. With the exception of some instances of allergic encephalomyelitis,[138] the antigenicity of the injected material had to be potentiated by means of an adjuvant, the commonest one used being a mixture of an extract of tubercle bacilli in a water-in-oil emulsion (Freund's adjuvant). The function of the adjuvant is not entirely clear and at least three explanations have been put forward: (a) that it imparts to the tissue homogenate a tuberculin-like property; (b) that it delays absorption of the homogenate from the site of injection; and (c) that it mobilizes and activates the mesenchymal cells, thereby increasing the chances of suitable mutations in the direction of forbidden clone formation.[157] The last explanation is the one most acceptable at present. It should be stressed that, for example, thyroid lesions could not be produced without an adjuvant, and even the existence of a lesion after injection of autologous thyroglobulin with Freund's adjuvant is still disputed.[151]

From a morphologic point of view, the common denominator of all these lesions is the proliferation and infiltration of immunologically competent cells in the target organ. In light microscopic studies tissue destruction and/or replacement follows the cellular reaction.[176] Since the lesions could not be produced by passive transfer of the appropriate circulating antibody[75] and since evidence has been produced that transfer of the experimental disease by immunologically competent cells was possible,[74, 130] the inescapable suggestion emerged that the proliferating cells were responsible for the parenchymal injury.

The role of transferred sensitized cells is in doubt. It has been suggested[176] that their function is to circulate and to respond to the presence of antigen by leaving the blood stream and there to proliferate. This interpretation is based on the finding[115] that delayed sensitivity is maximal from the

moment when transferred cells are injected into the blood stream.

From amongst the cells which invade or appear in the parenchyma, both in the primary experimental lesion and in the transfer experiments, histiocytes (macrophages) are singled out as the primary pathogenic agent. They are said to be capable of destroying the antigen-containing tissue by phagocytosis, by extracellular digestion, by formation of an unknown type of short-range antibody or by some other mechanism which is as yet unknown.[176] Plasma cells, the morphologic counterpart of antibody production,[117] are present in variable numbers in these lesions and their presence is thought to be of secondary significance.[129, 176]

The inability to transfer the experimental autoimmune diseases by means of circulating antibody[75] and the successful transfer by means of cells[130] has further suggested that the reaction in these lesions was *akin to tuberculin-type hypersensitivity* which can also be transferred in this way.[26] Rich[135] considered that death of tissues in such reactions was the result of the activity of the antigen on sensitive cells and that inflammation was secondary to necrosis. This classical view was challenged by Gell,[61] who considered that the perivascular mononuclear infiltration in the tuberculin reaction could precede necrosis. Dienes and Mallory[43] have shown that early and mild tuberculin reactions may not be accompanied by necrosis at all. In applying these thoughts to experimental autodestructive processes it is suggested that the invasive and destructive potential of the invading cells parallels the findings in tuberculin-type hypersensitivity reactions.[176]

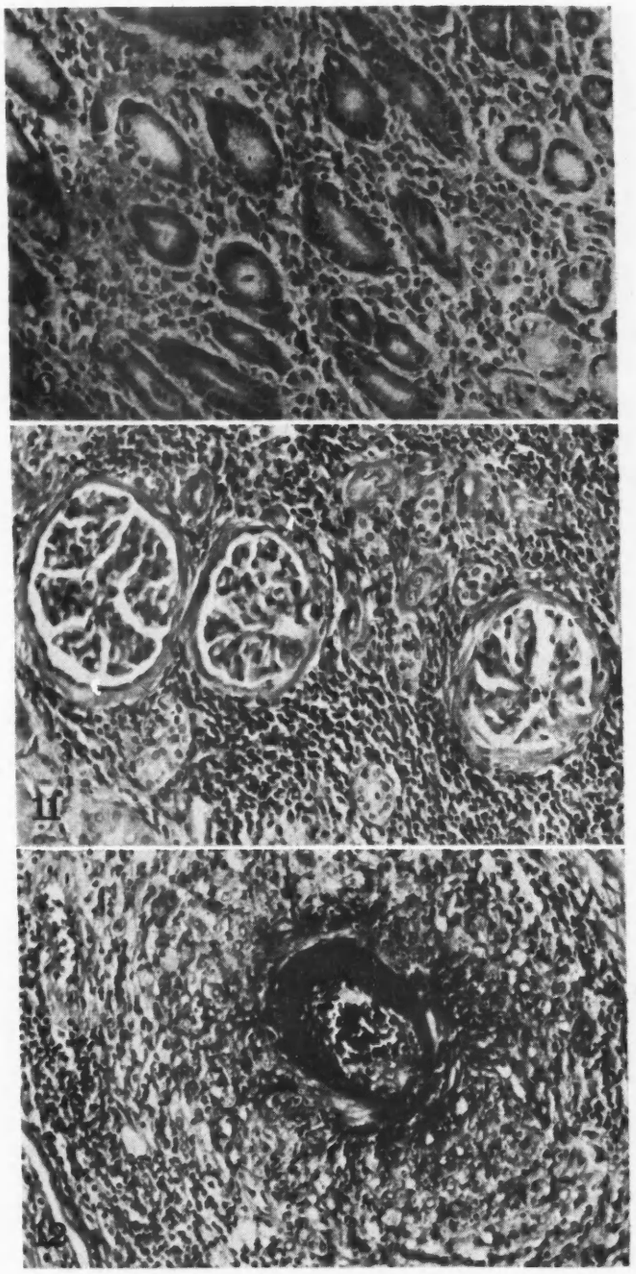
The evidence for the destructiveness of histiocytic cells is almost entirely circumstantial, based as it is on light microscopic studies. Subtle alterations of the parenchyma before invasion by cells and before actual morphologic evidence of necrosis have yet to be investigated by the newer methods available to the morphologist. It has also been suggested that in some locations massive proliferation of immunologically competent cells in the target organ may lead to separation of parenchyma from the capillary blood supply leading to an ischemic injury combined with pressure atrophy of the parenchyma.[156] All such speculations still leave unanswered the question of why immunologically competent cells display such an unfaltering affinity for the antigen-containing site.

Perhaps the most important consideration in assessing the value of the experimental prototype of autodestructive disease is the dictum that identity of lesions is no absolute proof of identity of etiology or pathogenesis.[137]

Significance of Immunologically Competent Cells

Whatever the exact relationship of the i.c.c.'s to the development of the lesions, the pathologist possesses as yet no definite criteria for diagnosing unequivocally an autodestructive process. Perhaps the only exceptions to this rule are erythrophagocytosis[19] and hematoxylin bodies, the morphologic counterpart of the LE phenomenon, in tissues.

It is axiomatic in the study of immunopathologic processes that all i.c.c.'s aggregate in tissues in response to antigenic stimulation. Accepting this concept, the pathologist distinguishes nevertheless



Figs. 10 to 12.—The pathologist's variable interpretation of immunologically competent cells in tissues is depicted in these three micrographs.

Fig. 10 shows their presence in the lamina propria of an intact stomach mucosa where they are not considered to be of any pathogenic significance. H. and E., × 304.

Fig. 11 shows their presence in the connective tissue of the kidney, the glomeruli of which show an ischemic injury associated with pyelonephritis. Their presence here is interpreted as evidence of chronic inflammation. H. and E., × 304.

Fig. 12 shows a necrotizing vasculitis in systemic lupus erythematosus in which the presence of immunologically competent cells is thought to play a role in the pathogenesis of the lesion. H. and E., × 261.

three varieties of immunologically competent cells. If they are present in tissues in the absence of any specific injury they are for practical purposes ignored (Fig. 10). If they form part of a cellular infiltration in response to an injury by a physical, chemical or biologic agent, their presence is considered as evidence of chronicity of the lesion (Fig. 11). In these circumstances where their presence in tissues is associated with a specific process which is known or suspected of being initiated or perpetuated by allergic mechanisms, the pathologist accepts the possibility that they may play a special role, directly or indirectly, in the initiation and/or perpetuation of the injury (Fig. 12). Just as the clinician and immunologist have come to distinguish potentially destructive from protective antibodies, so the morphologist has recognized that cells may possess a parallel divergence of potential. It is noteworthy that such cells, however, do not differ in appearance at either the light or electron microscopic level.[8]

(To be continued)

THE SELECTIVE VULNERABILITY OF THE BRAIN TO ANOXIA*

P. LAMPERT, M.D., *Toronto*

CERTAIN areas in the brain are more vulnerable than others to lack of oxygen. The grey matter is more susceptible than the white. The medulla and the spinal cord survive much longer than the cerebral cortex, just as the glial cells are more resistant than the nerve cells. This selective vulnerability to anoxia has been the cause of much discussion. The purpose of this report is to record a case of cerebral anoxia with lesions which in some respects do not follow the pattern usually seen in such cases, and to review some of the factors which might account for these findings.

A 17-year-old youth was employed to test gas masks. Owing to a mechanical failure, he accidentally breathed pure nitrogen for 7 to 10 minutes until he was found deeply cyanotic and unconscious. Though he was immediately given artificial respiration and put in an oxygen tent, he had several grand mal seizures and his blood pressure dropped to 80 mm. Hg systolic. On arrival at a local hospital he was found to be in a state of decerebrate rigidity. A tracheotomy was performed, and after a week without change in his condition he was transferred to the Toronto General Hospital. He was then unconscious, with flexed spastic extremities, upgoing toes and clonus of both ankles. No withdrawal on painful stimuli was observed. Repeated electroencephalograms (EEG) revealed almost complete absence of any cerebral activity. He was given adequate regular tube feeding but continued to lose weight, developed decubitus ulcers and finally died of bronchopneumonia without regaining consciousness four months after the accident.

Postmortem Findings

The cause of death was bronchopneumonia. The organs other than the lungs and the brain were unremarkable. The brain weighed 1200 g. There was marked narrowing of the cerebral convolutions with widening of the sulci, particularly over both frontal lobes. In the parasagittal regions of the parietal and occipital lobes the leptomeninges were brownish and the veins and the superior sagittal sinus in this region were occluded by brownish, friable, antemortem blood clot. The vessels on the base of the brain were normal. Coronal sections revealed moderate symmetrical dilatation of the ventricles. The caudate nucleus and putamen were shrunken and spongy on both sides. The globus pallidus revealed a few patchy, granular yellowish areas. The cerebral cortex appeared thinned throughout and a laminar granularity was apparent. Only the insular and temporal cortex appeared normal. The cerebellum and brain stem were unremarkable.

Microscopically, the cerebral cortex showed laminar necrosis involving mainly layers three and four, although in some areas all save the molecular layer were destroyed. Severe gliosis, numerous macrophages and vascular proliferation were observed in the region of the collapsed layers. The damage was more severe in the crest of the convolutions than in the depth of the sulci. The area striata of the occipital lobe, however, showed the most extensive destruction, affecting the depth of the calcarine fissure and the bordering crests to the same degree (Fig. 1).

The pyramidal cell layer of both Ammon's horns showed preservation of the Sommer's sector or area H_1, but area H_3 revealed a diffuse loss of cells and there was also an adjacent patchy loss of cells in the usually resistant area H_2 (Fig. 2). Complete loss of neurons and cavitation with accumulation of macrophages were noted in the putamen on both sides. The caudate nucleus showed equally severe involvement, although a portion adjacent to the ventricle remained relatively intact. Patchy cavitations and sponginess were observed in the globus pallidus bilaterally, but at the margin of these necroses, as well as occasionally in the centre, well-preserved nerve cells were noted, surrounded by macrophages and supported by remnants of a vascular network (Fig. 3). Complete loss of nerve cells was noted in the dorsomedial and anterior nuclei of the thalamus bilaterally. There was also loss of cells in the dorsal part of the ventral group of nuclei of the thalamus. The subthalamic nucleus, the hypothalamic nuclei, the lateral geniculate body, the inferior olivary and dentate nuclei were intact. The mammillary bodies revealed preserved nerve cells within a collapsed tissue full of macrophages. The zona reticularis of the sub-

*From the Division of Neuropathology, Department of Pathology, University of Toronto.

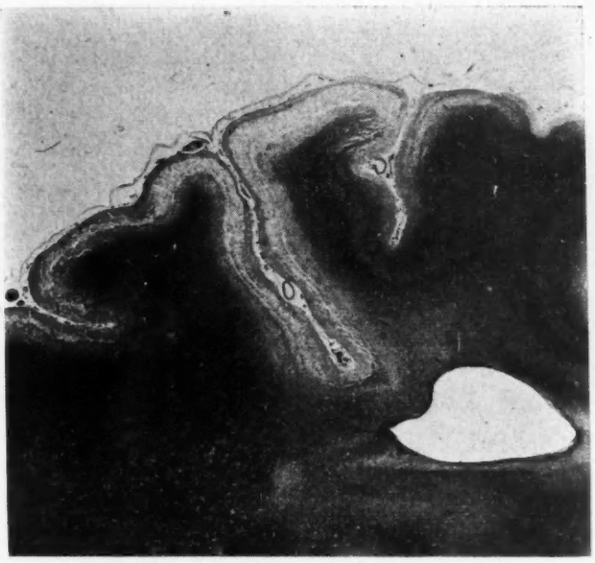


Fig. 1.—Visual cortex revealing severe laminar necrosis of the area striata but sparing of the cortex in the depth of the adjacent sulci. H. & E., × 5.

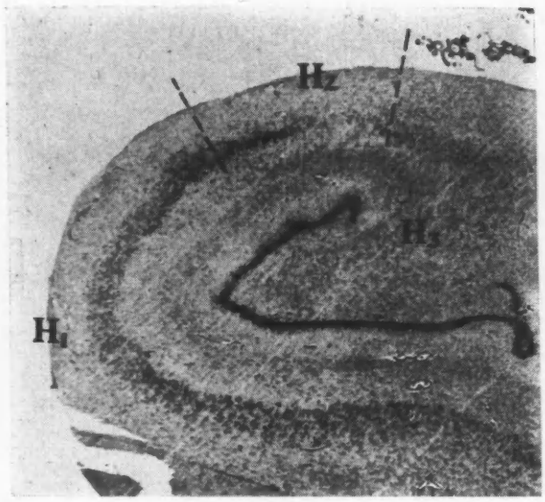


Fig. 2.—Ammon's horn showing preservation of area H_1, patchy loss of cells in H_2 and almost complete loss of nerve cells in H_3. C.V., × 8.5.

stantia nigra was intact. The zona compacta was well outlined owing to the abundance of macrophages in this region, and it was surprising to see a large number of well-preserved nerve cells in this area (Fig. 4). The cerebellar cortex showed well-preserved Purkinje cells which only in the depth of the foliae had disappeared in some regions.

The superior sagittal sinus and tributary veins revealed old, recanalized thrombi.

DISCUSSION

The illustrations depict features which are not commonly seen in cases of cerebral anoxia, namely involvement of the area striata of the visual cortex, together with predominant involvement of the crests of the cerebral convolutions; partial destruction of area H_2 of the Ammon's horn and preservation of area H_1 and—most unusual—good preservation of nerve cells within patchy necrotic areas of the globus pallidus and the zona compacta of the substantia nigra. Area H_1 of the Ammon's horn is generally considered to be most vulnerable to anoxia, and the resistance of areas H_2 and the area striata of the visual cortex has always been emphasized. The cerebellar cortex is usually found to be very vulnerable, whereas in this case only the depths of the foliae were involved. The opposite was noted in the cerebral cortex where the crests of the convolutions were severely affected and only in the depth of the sulci were preserved cortical layers identified.

Differences in the distribution of lesions due to cerebral anoxia have previously been described (Scholz[2]). It is known that certain forms of anoxia, such as occur in chronic anemias, and high altitude anoxia or carbon monoxide and cyanide poisoning affect regions in the brain which are more resistant to other types of anoxia such as that caused by sudden asphyxia, cardiac arrest or strangulation. An understanding of the variable factors responsible for this difference would appear necessary before one could interpret the unusual findings in this particular case.

Cerebral anoxia can be induced by lack of oxygen (anoxic anoxia), lack of oxygen carriers (anemic anoxia), stasis of blood (stagnant anoxia) or by poisoning of the respiratory enzymes (histotoxic anoxia). It is clear that stagnant anoxia or ischemia abolishes the supply not only of O_2 but also of glucose, as well as blocking the removal of metabolites. The effect of ischemia can therefore be expected to be different from the effect of simple anoxia. This is well demonstrated by the following experiment. When a subject is exposed to an atmosphere simulating that of high altitudes, one observes that unconsciousness develops 8 to 10 seconds after the oxygen tension of the blood has fallen to zero. After obstruction of both carotid arteries the same time elapses before the subject becomes unconscious. Therefore the loss of function takes place at equal speeds following anoxia and ischemia. However, the recovery of function occurs at a different pace. Consciousness and legible handwriting return within about 20 seconds after anoxia of 12 seconds' duration, but it takes between 1 and 8 minutes to restore these functions after ischemia of the same duration (Opitz and Schneider[1]). If anoxia is complicated by hypoglycemia, the recovery time after such an injury approaches that after ischemia. Combined lack of glucose and oxygen therefore induces changes which are not as readily reversible as those caused by anoxia alone, and irreversible damage occurs more rapidly in ischemia than it does after anoxia.

The vulnerability of the different areas of the brain to anoxia or ischemia could depend on their metabolic rate and the capacity to satisfy their basic energy requirements by anaerobic glycolysis. In ischemia the amount of glucose made available by local glycogenolysis and the quantity of accumulated metabolites interfering with anaerobic glycolysis are important additional factors. Empi-

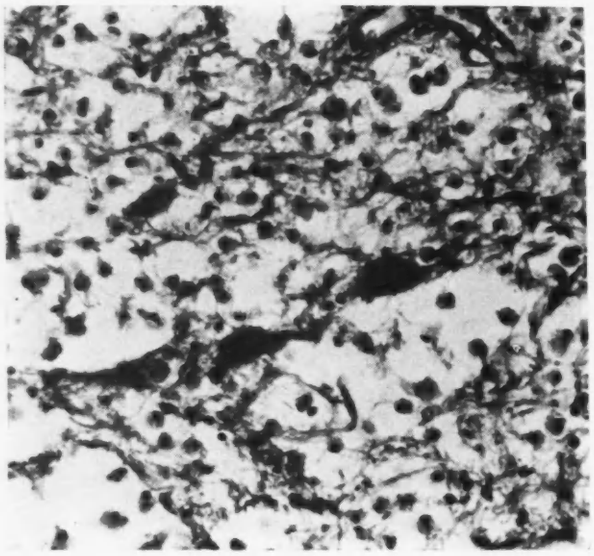


Fig. 3.—Preservation of a few nerve cells in areas of cystic necrosis of the globus pallidus. H. & E., × 270.

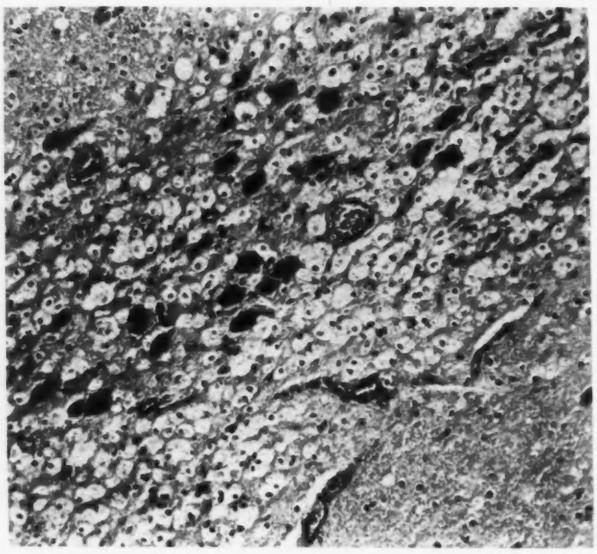


Fig. 4.—Preservation of nerve cells in severely damaged zona compacta of the substantia nigra. H. & E., × 135.

rically one finds that the vulnerability of the brain to ischemia consistently reveals a gradient from cerebral and cerebellar cortex and Ammon's horn to corpus striatum, globus pallidus and medulla. In anoxia unaccompanied by circulatory arrest such as might occur in anemia, carbon monoxide poisoning and high altitude anoxia, the basal ganglia show themselves to be more vulnerable, sometimes even without damage to the cerebral or cerebellar cortex (Scholz[2]). In every case of cerebral anoxia, associated general or local ischemia affects the distribution of the lesions. Before attempting to evaluate the role of ischemia in the case reported here, it is appropriate to review some of the facts which are known to be peculiar for the different areas of the brain and which might give a clue to their vulnerability to anoxia.

OXYGEN CONSUMPTION

The oxygen consumption of the normal adult brain is about 45 c.c./min. or about 15 to 20% of the body's total oxygen consumption. This rate remains relatively constant, i.e. even during maximal electrical stimulation only a moderate increase is observed as compared to an almost 20-fold increase of oxygen consumption of the skeletal muscle during maximal effort. The grey matter of the brain consumes five times as much oxygen as the white. Dixon and Meyer[3] measured the oxygen consumption of slices of different parts of the normal ox brain and report the following figures in μl./mg. wet weight/hour:

Cerebral cortex.....	1.70	Ammon's horn.....	1.26
Cerebellar cortex....	2.5	Thalamus.....	1.17
Corpus striatum.....	1.9	Globus pallidus.....	0.36

At first glance it might appear logical that areas with highest oxygen consumption would be most vulnerable. However, such is not the case. For instance, the retina of the rat has an oxygen consumption of 6.4 μl./mg. wet weight/hour. The cerebral cortex of the rat consumes 2.2 μl./mg. wet weight/hour. The retina loses its function after 5 to 15 seconds of anoxia but it can still be revived after 22 minutes. (Opitz and Schneider[1]). The cerebral cortex loses its function after 10 to 30 seconds and no revival is possible after 6 minutes of anoxia, indicating that the cortex is much more vulnerable than the retina, although the O_2 consumption of the latter is more than twice as high. The explanation for this discrepancy may be twofold. First, the oxygen consumption reflects the amount of oxygen used during normal cellular function. This amount does not necessarily parallel that required for the preservation of the structural integrity of the cell upon which revival after anoxia depends. Secondly, the oxygen consumption may depend on cellular density of the tissue. Indeed the retina contains many more cells per unit volume than does the cerebral cortex. One might expect that oxygen consumption calculated per one cell may correlate better with vulnerability to anoxia. Heller and Elliott[4] have done such a study and their figures for the cat brain are:

	Nuclei per c.mm. (thousands)	*Oxygen uptake in μl. per hr. per mg. weight*	*per 10^6 nuclei*
Cerebral cortex....	128	2.4	19
Cerebellar cortex...	808	2.1	2.6
Corpus callosum....	135	0.7	5.7

This reveals the surprising fact that the respiration per cell of the corpus callosum, which contains no nerve cells but mainly oligodendrocytes, is more active than the respirations per cell of the cerebellar cortex. Yet the vulnerability of the cerebellar cortex to most types of anoxia equals that of the cerebral cortex, whereas the corpus callosum is very resistant. However, it should be mentioned that demyelination associated with necrosis of oligo-

dendrocytes, localized particularly in the corpus callosum, has been noted after histotoxic anoxia, e.g. cyanide poisoning in rodents. Demyelination has also been described after carbon monoxide poisoning and high altitude anoxia. From all of these findings the conclusion may be drawn that although the oxygen consumption is a good indicator of the functional activity of the different areas of the brain, it is nevertheless not an absolute measure of their vulnerability to anoxia.

VASCULARITY

The length of the capillaries in the different regions of the brain expressed in mm./c.mm. is, according to Dunning and Wolff:[5]

Cortex	871	Pallidus	509
Striatum	640	White matter	374

Areas with the richest blood supply might be expected to be most vulnerable to anoxia or at least to ischemia. But again one has to investigate the question whether differences in vascularity are only an expression of the differences in the amount of energy utilized in functional activity rather than in that used to maintain cellular integrity. The comparison of the vascularity of the different areas with their cellular density reveals that the vascularity does not correspond to the number of cells but rather to the number of synapses. For instance, a comparison of the vascularity of the cortical laminae 1 and 4 with that of the trigeminal ganglion which contains no synapses shows a capillary length of 733, 857 and 547 mm./c.mm. respectively. The number of cell bodies found in sq. mm. in these areas is 334, 1826 and 452 (Dunning and Wolff[5]). The trigeminal ganglion with a higher cell count than lamina 1 of the cerebral cortex but with no synapses shows a much lower vascularity. Similarly, the rich vascularity of lamina 1 as compared with the disproportionately more cellular and only slightly more vascular lamina 4 can be related to its richness in synapses. Vascularity seems therefore to be another indicator of the functional peculiarities of different areas rather than a measure of their vulnerability. This is even more strikingly demonstrated by a correlation of the vascularity of the hypothalamic nuclei and their vulnerability to anoxia. The length of the capillaries in the nucleus paraventricularis and supraopticus is 2023 and 1960 mm./c.mm. respectively (Craigie[6]). Both nuclei are as a rule resistant to anoxia. Here, the comparatively very rich vascularity is presumably related to their neurosecretory function rather than richness in synapses.

CHEMICAL PROPERTIES

If neither the vascularity nor the oxygen consumption of the different areas of the brain explains the selective vulnerability, it must be assumed that the cells in the different areas possess biochemical qualities which are distinct from one area to another and might thus account for the difference in their vulnerability. This concept has always been stressed by C. Vogt and O. Vogt.

Areas rich in enzymes capable of promoting anaerobic glycolysis can be expected to be more resistant to anoxia than others. The importance of such enzymes is well demonstrated by the following data. The newborn rat survives anoxia for 50 minutes. The adult rat succumbs after three minutes. If, however, the newborn rat is given iodoacetic acid or fluorides, it dies as quickly as the adult rat under the same conditions. These poisons inhibit enzymes necessary in the process of anaerobic glycolysis. The newborn rats so treated show necrosis of neurons in the brain stem, indicating that these regions are capable of sustaining life by anaerobic glycolysis at this age (Hicks[7]). The resistance of the medulla to anoxia in the adult might therefore be explained by a greater abundance of such enzymes in this region.

A prerequisite for anaerobic glycolysis is, of course, the presence of glucose. The energy derived from one molecule of glucose by aerobic glycolysis is much higher than that obtained by anaerobic glycolysis. In anoxia, therefore, a greatly increased amount of glucose must be made available to satisfy the energy requirement of the different areas of the brain. Additional glucose may be derived by local glycogenolysis. Huszák[8] felt that only the glycogen of the white matter can be utilized. This would thus provide the white matter with an extra protection against anoxia. Hiestand and Nelson[9] found that hyperglycemia can prolong the anoxic survival time. An area which contains less blood might be expected to run out of glucose more rapidly. Less vascularized areas might thus become more vulnerable to anoxia. For the same reason any complicating local ischemia, even of a transient nature, may become a decisive factor in determining the vulnerability of such an area.

In addition to vascular occlusion by thrombus or embolus, local ischemia can be the result of vascular compression or vasospasm. Any severe injury to the brain is rapidly followed by edema, and the swollen brain may compress first the veins and later the arteries. An associated drop in blood pressure would enhance such a compression. Lindenberg[10] has reviewed the sites of predilection of lesions caused by such a mechanism. He mentioned the compression by the edge of the tentorium of the posterior cerebral artery and of the long branch supplying the area H_1 of the hippocampus. The pallidal branches of the anterior choroidal artery are also, according to Lindenberg, within the range of the rostral part of the tentorial edge, which may explain the selective necrosis of parts of the globus pallidus. Also, narrowing of the interpeduncular fossa and wedging of the mammillary bodies into this fossa may affect arterial branches going to the thalamus. The other factor complicating anoxia—vasospasm—has been investigated by Scholz.[2] He

demonstrated that sudden asphyxia after obstruction of the trachea in cats caused focal areas of anemia and venous stasis, mainly in the cerebral and cerebellar cortex, which he explained by vasospasm. He emphasized that suddenness of the asphyxia is important in order to obtain such lesions in the cortex.

In view of the ideas reviewed in the preceding paragraphs, it is suggested that some of the unusual findings of the case presented in this paper can be explained by a complicating factor of secondary ischemia. The severe involvement of the crests of the convolutions could be the result of compression of these regions against the dura, owing to generalized swelling of the brain. The involvement of the occipital cortex could have followed the pressure on the posterior cerebral artery against the edge of the tentorium. Since the onset of anoxia was very abrupt, vasospasm might have occurred, leading to patchy loss of nerve cells in the hippocampus. Finally, the drop in the patient's blood pressure, recorded in the history, might have facilitated all these events.

The thrombosis of the superior sagittal sinus and its tributary veins, which might have contributed to the cerebral edema, is another uncommon finding in anoxia. Thrombosis of the sagittal sinus after operations or childbirth has been observed. It is possible that the severe injury to the brain in this case may have acted as a similar stress to favour clotting of the blood.

The preservation of nerve cells in otherwise severely damaged tissue remains to be discussed. Damaged nerve cells with eosinophilic homogeneous cytoplasm adjacent to completely normal-looking cells in the cerebral cortex is often the only morphological evidence of cerebral anoxia or hypoglycemia in cases with short survival. It is conceivable that not all cells in an area are at work simultaneously and that lack of oxygen affects active cells more than others. This view is stressed by the observation that regions such as the precentral gyrus exhibiting great activity at the time of anoxia are often found to be particularly vulnerable. Scholz has coined the term "consumptive anoxia" for this phenomenon which undoubtedly plays a role in the selective vulnerability or resistance of the brain to anoxia.

SUMMARY

Factors responsible for the selective vulnerability of the brain to anoxia are discussed. Oxygen consumption, vascularity and chemical properties vary considerably from one area of the brain to another. A difference in the vulnerability to anoxia or ischemia is apparent. The effects of secondary ischemia on the distribution of the lesions in cases of anoxia are emphasized and explain some of the unusual features in a case of cerebral anoxia with four months' survival.

The author wishes to thank Dr. T. Van Patter, Pathologist, St. Michael's Hospital, Toronto, for permission to study this brain, and Dr. J. Olszewski, Professor of Neuropathology, University of Toronto, for suggestions and help in editing.

REFERENCES

1. OPITZ, E. AND SCHNEIDER, M.: *Erg. Physiol.*, **46:** 126, 1950.
2. SCHOLZ, W., editor: Erkrankungen des zentralen Nervensystems, *In*: Handbuch der speziellen pathologischen Anatomie und Histologie, Vol. 13, Part I-B, edited by O. Lubarsch, F. Henke and R. Rössle, Springer-Verlag, Berlin, 1957, p. 1284.
3. DIXON, T. F. AND MEYER, A.: *Biochem. J.*, **30:** 1577, 1936.
4. HELLER, I. H. AND ELLIOTT, K. A.: *Canad. J. Biochem. & Physiol.*, **33:** 395, 1955.
5. DUNNING, H. S. AND WOLFF, H. G.: *J. Comp. Neurol.*, **67:** 433, 1937.
6. CRAIGIE, E. H.: *A. Res. Nerv. & Ment. Dis., Proc.* (1939), **20:** 310, 1940.
7. HICKS, S. P.: *A.M.A. Arch. Path.*, **55:** 302, 1953.
8. HUSZÁK, I.: *Biochem. Ztschr.*, **312:** 315, 1942.
9. HIESTAND, W. A. AND NELSON, J. W.: *Proc. Soc. Exper. Biol. & Med.*, **59:** 258, 1945.
10. LINDENBERG, R. J.: *J. Neuropath. & Exper. Neurol.*, **14:** 223, 1955.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

ONTARIO MEDICO-POLITICS

Now that the session of the Ontario provincial legislature is over, things have quieted down in the medical world, and all are waiting to see what the next move of the Medical Council will be. It is suggested that it will in all probability endeavour to square itself with the public and initiate reforms too long delayed. The failure of the government to make the radical changes asked for in the "University Bill." was not overlooked by those who know the personnel of the cabinet, and it is evident that the question assumed a political importance not anticipated at one time. The subject is not dead, and the solution of the difficulty may be found in the appointment of a medical commission, as in Ontario they seem to adopt the commission idea as the simplest method of getting over any difficulty.

The premier apparently recognizes the fact that there are wrongs to right, and if he is once convinced that the situation is serious, he will act promptly; but the difficulty is in getting him to view medical questions from the standpoint of medicine. His attitude in regard to tuberculosis did not excite the admiration of the world of medicine; and the fact that he recently presided at a Christian Science meeting has excited some comment. Possibly it was a case of political exigency.

Now that Dominion registration is in sight it will be interesting to learn how anxious Ontario really is to become one of the confederation. The medical student is naturally anxious for its immediate development, and if it results in the establishment of a central examining body, independent of the provincial councils, such a change will be welcomed by many. What the attitude of the Medical Council will be is another question; especially if it believes that it will prevent students from appearing before it for examination.

Medical inspection of Toronto schools is a step in the right direction; let us hope that the best qualified persons will be found for the positions.—Editorial, *Canadian Medical Association Journal*, 1: 457, May 1911.

Canad. M. A. J.
May 27, 1961, vol. 84

RESERPINE—A COMPARISON OF CHRONIC TOXICITY IN ANIMALS WITH CLINICAL TOXICITY

J. M. PARKER, M.D., Ph.D.*‡ and
C. W. MURPHY, M.D.,†‡ *Montreal*

THE TOXICITY of substances destined for human therapeutic use is determined in the first instance by their toxicity in animals. The failure of such studies to predict in detail the side effects later to be encountered in man justifies an examination of proposals made to improve this situation. The purpose of the present paper is to examine one such proposal recently made; it was suggested[1] that more information would be obtained if chronic toxicity studies—that is, the feeding or daily administration of materials to animals—were prolonged: for drugs that might be purchased over the counter, the studies should be extended to two years in rats and dogs; for prescription drugs used in the treatment of chronic diseases, they should be extended to one year in rats and six months in dogs. The underlying assumption for this suggestion is that this is the best way to utilize animals and time, and that more information will be obtained the more the study time is prolonged. As a test for this assumption it was decided to review the history of a drug for which both animal and clinical data were available, in order to see to what extent the toxicity and pharmacological studies undertaken before its introduction were predictive of its later side effects in humans.

Reserpine, the drug which was chosen for this study, was submitted to the Food and Drug Directorate for permission to introduce in 1953, with data relating to 10-12 weeks' chronic toxicity testing in rats, dogs and monkeys, together with pharmacological and clinical data which will be reviewed in this report. Most of the side effects of reserpine will be seen to have been closely related to its pharmacology, and those side effects which are not will be shown to have been unpredictable from animal toxicity studies.

In 1931 Sen and Boss published in the *Indian Medical World* an account of "a new Indian drug for insanity and high blood pressure".[2] They showed that whole Rauwolfia root reduced blood pressure and controlled mania. In 1952 the alkaloid reserpine was identified.[3] In the same year, clinical trials were begun. In 1953 it was marketed as a tranquillizer for general use and as an antihypertensive agent, with recommended doses in adults in the range of 1-4 mg. daily by mouth. Within a year further clinical studies led to its recommendation for use in major psychiatric conditions at much higher dose levels, viz. 5-20 mg. orally and by injection daily.

*Charles E. Frosst & Co., Montreal, Que.
†CIBA Company Limited, Dorval, Que.
‡Members of Committee on Chronic and Clinical Toxicity Correlation, Pharmacological Society of Canada.

The most common side effects of reserpine (nasal stuffiness, drowsiness and diarrhea) were known at the time of its introduction. As clinical experience with the drug grew, the other side effects now known to be associated with reserpine, and which proved on the whole to be more serious, although less frequent, were reported. In 1954, bleeding peptic ulcer,[4] parkinsonian-like symptoms[5] and mental depression[6] were reported. In 1956, cases of gynecomastia and lactation were noted[7] and deaths following electroconvulsive therapy in patients receiving reserpine were reported.[8] Many of these side effects were now realized to be related to dosage, so that the principal pharmaceutical manufacturers recommended a lowering in dosage to 0.1-1.0 mg. per day, orally, in the treatment of hypertension and conditions requiring mild tranquillization.

KNOWN PHARMACOLOGY AT TIME OF INTRODUCTION

The New Drug Submission for reserpine was made to the Food and Drug Administration, Department of National Health and Welfare, Ottawa, in 1953. In addition to the usual contents of a submission relating to methods of manufacture, quality control, claims and clinical investigations, that part of the submission dealing with pharmacology and toxicology consisted of the reprints of eight papers, together with additional unpublished studies. The pharmacology studies, performed for the most part in animals, showed that reserpine was a sedative-hypnotic, producing a sort of sedation that differed from barbiturates, that it did not anesthetize, and was not anticonvulsant (this new form of sedation was called "tranquillization"). Reserpine was shown to inhibit excitation from caffeine or morphine. It was further shown that reserpine was hypotensive, produced miosis, accelerated peristalsis, and had an effect on the temperature regulation centre. There was a delay in action even after intravenous administration (from two to four hours) and prolonged effects, lasting in dogs for seven days, were seen after an oral dose of 0.1 mg./kg. In man, weight gain was seen to occur. The conclusions drawn at this point were that these actions implied central depression of sympathetic effects and effects on the thalamopituitary pathways (it was not until 1955 that papers began to appear showing the interaction between reserpine and serotonin).[9]

KNOWN TOXICOLOGY AT THE TIME OF SUBMISSION

Rats

Acute doses of 2 g./kg. orally produced no deaths, but did cause sedation, tremors and a rough coat. Administration of 10 mg./kg. intravenously caused death with ataxia, dyspnea and sedation. Chronic administration in rats was carried on for more than two months by gavage. At a dose level

of 2 mg./kg. rats were sedated but no toxic symptoms were seen. With 4 mg./kg., more sedation was apparent, one death occurred, and at this dose rats failed to gain weight. At 8 mg./kg. the animals showed profound sedation with cachexia. There was no evidence of diarrhea, but all the animals were dehydrated. Deaths occurred at this dose level, but it could not be determined whether the deaths were due to a direct toxic effect of reserpine or whether they resulted indirectly from the profound sedation which interfered with regular food intake.

Dogs

The acute administration of 100 mg./kg. intravenously produced relaxation of the nictitating membrane, miosis, diarrhea and sedation. Death was produced by 500 mg./kg. in half the animals, with panting, salivation, tremors, lethargy and profuse diarrhea. Chronic administration in dogs, over a three-month period, using much lower doses (10-50 μg./kg.), produced sedation, miosis, tremors and profound gastrointestinal disturbances ranging from diarrhea to ulcerations of the lips due to licking (the gastrointestinal system of dogs was subsequently shown to be particularly sensitive to the influence of reserpine). Reserpine was also shown in dogs to cause an increase in gastric secretion.

Monkeys

Repeated daily, an oral dose of 1 mg./kg. produced sedation, a drop in rectal temperature and depressed activity. The animals (rhesus monkeys, very wild under untreated conditions) became very easy to handle. Administration of 1 mg./kg. intravenously produced profound sedation; 500 μg./kg., intravenously, produced sedation, tremors and shivering; and when the same doses were repeated three days later, profound sedation occurred 10 minutes after the injection. Very little effect on the gastrointestinal system was noted.

Side Effects in Humans

After reserpine became available for clinical investigation, and particularly after reserpine began to be studied in high dosages in psychiatric conditions, the side effects in humans became apparent. Nasal stuffiness, sluggishness and increased frequency of bowel movements were quickly established as the principal side effects, and these were all apparent at low doses. Other side effects, already mentioned,[4-8] were slower to appear.

Concerning the incidence of side effects, information is available from a world-wide survey made by the CIBA Company from May to September, 1957.[10] Physicians were asked to fill out five questionnaires, one for each of the last five patients they had treated for more than one month with reserpine for any indication. The questionnaire obtained data on use, results, therapeutic effects and side effects, all of which were analyzed by computer.

TABLE I.—PATIENT POPULATION CHARACTERISTICS

Sex:	male 2581 = 41.8%		female 3588 = 58.2%	
Age:	0 to 20 years	*160*	2.6%	
	21 to 40 years	*943*	15.3%	
	41 to 60 years	*2983*	48.3%	
	Over 60 years	*2083*	33.8%	
Diagnosis:	Hypertension		*5382*	87.2%
	Anxiety and tension		*1794*	29.1%
	Tachycardia or other heart diseases		*665*	10.8%
	Dermatology		*61*	1.0%
	Pediatrics (emotional disturbances)		*85*	1.4%
	Alcoholism		*92*	1.5%
	Menopausal disorders		*408*	6.6%
	Other		*194*	3.1%

The findings are given in the accompanying tables. Table I lists the patient population characteristics.

TABLE II.—DURATION OF TREATMENT OF ALL PATIENTS

Less than 2 months	*985*	16.0%
2 to 4 months	*1498*	24.3%
4 to 8 months	*1248*	20.2%
8 to 12 months	*707*	11.4%
1 year or more	*1718*	27.9%
Not stated	13	

Table II shows the duration of treatment: over 80% of the patients received treatment for more than two months.

Of the side effects noted, nasal stuffiness was the commonest (13%). Fatigue and lethargy occurred in 9%; gastric disorders in 3%; diarrhea in 3%; headaches in 3%; psychic depression in 1.2%. Parkinsonism was extremely rare, occurring only in three patients. Compared to the experience in psychiatry, where larger doses are used in general, it can be seen that both gastric side effects and parkinsonism were rare when doses below 1 mg. were used.

Since the most important side effect of the Rauwolfias is depression, more attention will be paid to it here than to the other side effects. Psychic depression, which was reported in 1.2% of the cases, occurred more commonly in Britain, Australia and Canada than one would expect to be the case by chance. This may have been due to the tendency to give larger initial doses (1 mg. or more) in these countries. The risk of developing depression increased with age, as is shown in Table III.

TABLE III.—AGE OF PATIENTS SHOWING DEPRESSION

	Cat. 1	*Cat. 2*	*Total*	%
Under 40 years...	5	3	8	10.5
40 to 60 years....	22	19	41	54.0
Over 60 years....	11	16	27	35.5

Risk calculated in proportion to total number of cases in each age group

Under 40 years	0.72%
40 to 60 years	1.34%
Over 60 years	1.29%

Two categories could be determined. Category 1: temporary symptoms where treatment was not interrrupted, and Category 2: non-temporary symptoms where treatment had to be interrupted.

TABLE IV.—DURATION OF TREATMENT
(PATIENTS WITH DEPRESSION)

	Cat. 1	*Cat. 2*	*Total*	*%*
Less than 2 months.	6	2	8	10.5
2 to 4 months.....	9	9	18	23.7
4 to 12 months.....	8	12	20	26.3
1 year or more.....	15	15	30	39.5

For category 2:
Risk calculated in proportion to total number of patients in each duration-of-treatment group

Less than 2 months	0.20%
2 to 4 months	0.60%
4 to 12 months	0.61%
1 year or more	0.87%

With regard to duration of treatment, 90% of those with depression became depressed after more than two months of therapy. This is illustrated in Table IV. The risk became four times greater if treatment was continued over one year.

When the maintenance dosage of reserpine was considered, it was found that the risk was three times greater with doses of 1 mg. or higher. This is outlined in Table V.

TABLE V.—MAINTENANCE DOSAGE IN DEPRESSION CASES
Categories 1 and 2

	Cat. 1	*Cat. 2*	*Total*	*%*
Less than 0.20 mg...	4	0	4	5.3
0.20 mg. - 0.49 mg...	16	10	26	34.2
0.50 mg. - 0.99 mg...	13	20	33	43.4
1 mg. or more.....	5	6	11	14.5
No indication.....		2	2	2.6

Risk calculated in proportion to total number of patients in each dosage range

Less than 0.20 mg.	0.62%
0.20 mg. - 0.49 mg.	1.08%
0.50 mg. - 0.99 mg.	1.51%
1 mg. or more.	1.75%

However, even among these patients depression was rare and it is therefore likely that other factors, such as a predisposition to depression, were important in the development of this side effect.

DISCUSSION

The chronic toxicity data presented in the new drug application for reserpine related to studies carried out over a period of two to three months. Many of the side effects encountered later in man were anticipated by this time, although equal or greater contributions to this understanding were made by the pharmacological studies. Most of the unanticipated side effects would not likely have been uncovered by prolonging the chronic toxicity studies in animals. The following comparisons will illustrate this point.

Nasal Stuffiness

This, the most frequent side effect, was not commented on during the animal studies. Once it was reported from the first studies in man, it was easily demonstrated in animals.

Lethargic State

Animal behaviour was found to correspond with a similar effect in man. It was equally possible to show that the higher the doses of reserpine used the more profound this state of lethargy was likely to become.

Diarrhea

As a result of the parasympathetic-like action of reserpine, demonstrated in many pharmacological experiments, and also of the occurrence of diarrhea in animals, particularly dogs, this side effect was anticipated. A species differentiation had been noted, however, between various animals, and this side effect is less severe in man than in dogs.

Parkinsonian-like Syndrome

Tremor and increased salivation were noted in animals, but the parkinsonian-like syndrome was not seen. Its occurrence has been associated only with the higher doses used in psychiatry, but it is in any case doubtful if it could have been revealed by animal toxicity studies, since Parkinson's disease is notoriously difficult to reproduce in the experimental animal.

Peptic Ulcer

Experimental studies in animals before introduction and in animals and man after introduction[11, 12] revealed generally an increased gastric secretion of HCl, although in at least one study (0.75 mg. daily by mouth)[13] no change in man was noted. Reserpine has even been used as an adjunct to the treatment of peptic ulcer.[13, 14] Nevertheless, although the possibility of causing an exacerbation of peptic ulcer was not in fact shown on the basis of pre-introductory studies, this possibility could have been suspected on the basis of the gastric secretion studies and the knowledge of the generally parasympathetic-like activity of the drug.

Depression

This side effect could not have been foreseen as a result of animal studies, pharmacological or toxicological. The sluggishness and lethargy produced by the drug were discernible in animals, but psychic depression does not have a counterpart in animals.

Thus it is seen that on the basis of the two to three months' toxicity studies, the side effects of sluggishness and diarrhea were noted and were predictable in man. Nasal stuffiness could have been seen had it been suspected and looked for prior to reports from man. Peptic ulcer might have been suspected had gastric secretion studies been performed in man prior to introduction. In any case, predictability of this side effect would have resulted from pharmacological experiments and not from classical toxicity studies. Depression and the parkinsonian-like syndrome were unpredictable on the basis of animal studies.

Canad. M. A. J.
May 27, 1961, vol. 84

In a sense the results of this review are not surprising. Animal studies cannot completely parallel clinical usage. When a drug is destined for use either in a particular age group or in a specific disease, human toxicity may find no counterpart in the animal. In the present case, reserpine was destined primarily for use in hypertension and, therefore, confined at the beginning to patients who were on the average over 40 years of age. The most important, although not the most frequent, side effect of reserpine is depression, which has no counterpart in animals.

In reviewing the animal studies it is apparent that knowledge of the pharmacology of reserpine probably provided more information than chronic repeated dosing of compound. It is difficult to believe that more prolonged studies in animals by repeated dosage would have resulted in any further indication of future human toxicity. Admittedly, by present standards, the duration of animal toxicity studies was relatively short (three months) but other data submitted to the Canadian Government included pharmacological and clinical studies. All three aspects were important, but it seems that the two most important were pharmacological, giving an indication of the side effects one might expect as a result of the parasympathetic-like action of reserpine, and the clinical data, which gave a guide for human dosage, in addition to revealing the therapeutic usefulness of the compound. In a review of chronic toxicity testing techniques, Barnes and Denz[15] make a strong plea for not continuing such studies longer than three months. Rather than prolonging the long-term feeding experiments, they advocate investigating the mode of action of a new drug and how it behaves in man. The present authors would like to associate themselves with this plea, and believe that in the case of one drug at least, reserpine, the advantage of this has been shown.

SUMMARY

A review of the new drug submission on reserpine revealed that the most frequent side effects encountered in clinical trials were predicted from animal studies, and that carefully conducted quantitative studies of pharmacological effects in both man and animals were the most useful methods for such prediction. The actual doses and limits of dosages for man could only have been defined by clinical trials, such as those which were performed.

It would seem that, at least in the case of reserpine, toxicity studies prolonged for more than three months would not have been more predictive of human toxicity than the studies, both toxicological and pharmacological, reviewed here.

The authors would like to thank the following: Dr. C. A. Morrell, Director of the Food and Drug Directorate, who lent encouragement to this review and negotiated with the CIBA Company Limited, Canada, to make their new drug submission available for study; the CIBA Company Limited, Canada, for their report "International Inquiry on Serpasil among General Practitioners"; Dr. J. K. W. Ferguson, Director, Connaught Medical Research Laboratories, for his interest and stimulation in initiating this study.

REFERENCES

1. LEHMAN, A. J.: *Bull. Parenteral Drug A.*, **13**: 2, May-June, 1959.
2. SEN, G. AND BOSS, K. C.: *Indian M. World*, **2**: 194, 1931.
3. MUELLER, J. M., SCHLITTLER, E. AND BEIN, H. J.: *Experientia*, **8**: 338, 1952.
4. PELNER, L.: *J. A. M. A.*, **156**: 736, 1954.
5. WEBER, E.: *Schweiz. med. Wchnschr.*, **84**: 968, 1954.
6. FREIS, E. D.: *New England J. Med.*, **251**: 1006, 1954.
7. BORENSTEIN, P., DABBAH, M. AND BARÉ, D.: *Ann. Médicopsychol.*, **114**: 545, April 1956.
8. BRACHA, S. AND HES, J. P.: *Am. J. Psychiat.*, **113**: 257, 1956.
9. BRODIE, B. B., PLETSCHER, A. AND SHORE, P. A.: *Science*, **122**: 968, 1955.
10. CIBA Company Limited: International inquiry on Serpasil among general practitioners.
11. BARRETT, W. E., RUTLEDGE, R. A. AND ROGIE, B.: *Fed. Proc.*, **13**: 334, 1954 (abstract).
12. CLARK, M. L. AND SCHNEIDER, E. M.: *Gastroenterology*, **29**: 877, 1955.
13. DRENICK, E. J.: *Am. J. Digest. Dis.*, **1**: 521, 1956.
14. HOFFMANN, C. R.: *Am. J. Gastroenterol.*, **29**: 187, 1958.
15. BARNES, J. M. AND DENZ, F. A.: *Pharmacol. Rev.*, **6**: 191, 1954.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE GENERAL PRACTITIONER

A journal which is content to publish papers which emanate from the laboratory of a medical school, or the clinic of a general hospital, reflects very inadequately the medicine of a country so varied as Canada. In the *Western Medical News* for January, Dr. R. Woods of Leduc, Alberta, cites the case of a patient whom he was called upon to attend, and he addresses the pointed enquiry to the profession at large: "How would you conduct this case alone and single-handed, fifty miles from assistance and nothing but foreign-speaking people to irritate you by talking and saying nothing you could understand?" The case in question was that of a woman whom he delivered successfully of a hydrocephalic child with "a head about the size of a six year old boy's." Dr. Woods resorted to the expedient of applying the long forceps to the head, clamping them tight and tying them. Then he "allowed the labour to continue without further interference. Head with forceps clamped on was delivered after about three hours' time." We should like to address another enquiry to the profession: "What better could the most expert obstetrician have done?"

In the same communication Dr. Woods cites another successful case in which, after forty-eight hours, the cord was prolapsed and pulseless, the sac was destroyed, the face presented, and a large head was driven firmly into the brim of the pelvis. The patient had had for twenty-four hours the services of an amateur midwife, but according to Dr. Woods' account they were not very valuable: "She ruptured the sac with a large pair of scissors, and then, feeling something high above the brim, she pulled on it a little."

Such a relation as Dr. Woods makes is of incalculable value, since it gives to the universities a fresh apprehension of the difficulties which their graduates have to cope with, and to teachers a new incentive for sound instruction and thorough training.—Editorial, *Canadian Medical Association Journal*, 1: 455, May 1911.

HYPERURICEMIA AND ACUTE GOUTY ARTHRITIS PRECIPITATED BY THIAZIDE DERIVATIVES*

A. ARONOFF, M.D., F.R.C.P.[C]† and
H. BARKUM, M.D.,‡ *Montreal*

CHLOROTHIAZIDE has recently been shown to be a potent oral diuretic agent[1] with an important antihypertensive effect[2] when given in conjunction with other hypotensive agents. In addition to its saluretic action, it has a tendency to produce potassium depletion[3] and ammonia retention.[4]

More recently a number of authors[3, 5, 10, 23] have shown that there is a tendency towards elevation of the serum uric acid concentration in patients receiving chlorothiazide in the treatment of hypertension or congestive failure, and that this is due to a decreased clearance of urate by the renal tubules.[5]

Serum uric acid levels in the range of 3 to 20 mg. % have been observed in such patients but these have not been associated with overt evidence of gout.

In the past 18 months we have had the opportunity to observe six patients who developed acute gouty arthritis while receiving chlorothiazide. Eight additional cases of similar nature have been reported in the recent literature.[8, 10-13]

This paper comprises a report of 14 cases of gout precipitated by chlorothiazide. Their major features will be noted in an attempt to determine whether a characteristic clinical pattern or predisposing factor exists in these cases; several studies will be described which were carried out to assess the efficacy of uricosuric agents in decreasing serum uric acid levels while patients remain on chlorothiazide; and speculation concerning the factors which may contribute to the precipitation of overt gout will be discussed in the light of the disturbances in homeostasis induced by the thiazide derivatives.

CLINICAL FEATURES

All patients received either chlorothiazide or hydrochlorothiazide.

Of the 14 patients, 12 were men and two were menopausal women. Their ages varied from 40 to 80 years.

Six patients had a past history of gout but had been free of attacks for from one to five years. Eight patients had a negative past history and family history of gout, the first attack occurring while they were receiving chlorothiazide.

Eight patients were being treated for hypertension; of these, two had a positive history of gout and six had a negative history of gout. Six patients were under treatment for congestive heart failure; of these, four had a positive history of gout and two gave a negative history of this disease.

The onset of acute gout in relation to the beginning of chlorothiazide therapy was classed as early or late. Early onset occurred within three days to three weeks and was noted in eight cases; late onset occurred within three to ten months and was observed in six cases.

With regard to the relationship of the dose of thiazide to the onset of gout, the smallest dose used was 0.5 g. of chlorothiazide daily. On this dosage gouty arthritis occurred within three weeks to six months after chlorothiazide therapy was instituted. With the larger dosage of 1 g. b.i.d. acute gout occurred three days after beginning chlorothiazide therapy in several cases, and in 3 to 10 months in the others.

After the patient had one attack of gout, readministration of the drug precipitated a second attack after a shorter period of exposure.

Uric acid levels when symptoms of gout were present ranged from 5.8 mg. % to 12.7 mg. %.

With regard to the relationship of chlorothiazide therapy to the production of diuresis, four patients with congestive cardiac failure who showed a marked diuresis on chlorothiazide suffered the earliest onset of gouty arthritis at three, three, seven and seven days respectively. Among 10 patients, most of whom were hypertensive, who had no diuresis on chlorothiazide, the earliest attack occurred on the 13th and the 14th day.

Colchicine produced adequate relief of gouty symptoms whenever it was administered. Cessation of thiazide administration was followed by a reduction in serum uric acid levels in all patients but one who had associated renal disease. Phenylbutazone alone was given to four patients for whom it was relatively ineffective in relieving the manifestations of acute gout.

Uricosuric agents were employed in an effort to decrease the uric levels while the patients remained on chlorothiazide. Probenecid was administered to eight patients in all; in four of these a sustained lowering of the serum uric acid level was observed over a period of one to two weeks; three showed a transient lowering of serum uric acid level, and one patient showed no response. Zoxazolamine was used in one instance in which no lowering of the serum uric acid level was observed while the patient remained on hydrochlorothiazide. Five patients received no uricosuric agents.

To summarize the clinical features of this group of 14 patients:

Males were more commonly affected than females.

Eight patients had no previous history of gout; two of these were postmenopausal women.

The shortest interval between the beginning of chlorothiazide therapy and the onset of gout was observed in four patients with congestive failure

---

*Presented in part at the Second Canadian Conference on Rheumatic Diseases and at the Royal College of Physicians and Surgeons, Ottawa, January 1960.

†Department of Medicine and Arthritic Service, Queen Mary Veterans Hospital and Royal Victoria Hospital, Montreal.
‡Staff Physician, Ste.-Anne de Bellevue Hospital, Ste. Anne de Bellevue, Que.

who experienced a marked diuresis when chlorothiazide was administered. Three of these had a previous history of gout.

Those patients with a past history of gout who did not have a diuretic response to chlorothiazide developed symptoms later in the treatment program.

Though it is not safe to generalize from results in a small group of patients, it would appear that gouty symptoms in association with chlorothiazide therapy may be more readily expected in:

1. Males with and without a past history of gout.
2. Those who are on larger doses of thiazides.
3. Those who develop a marked diuresis while on thiazide therapy.

Most patients will respond to the classical treatment for acute and chronic gout with colchicine even though chlorothiazide therapy is continued. Where the clinical condition permits, cessation of thiazides will result in a prompt lowering of the serum uric acid levels. When it was undesirable to discontinue chlorothiazide therapy, an attempt was made to lower the serum uric acid levels with uricosuric agents.

Short-term experiments, using clearance techniques for periods of four hours[10] and 24-hour urine excretion studies, show that the uricosuric agents, probenecid, sulfinpyrazone and zoxazolamine may increase the uric acid clearance while patients remain on thiazide derivatives. It has not been shown that this effect will be sustained during prolonged administration of a uricosuric drug. In fact, three of the patients in this series showed only a transient lowering of serum uric acid levels and two showed no response in this regard while on continued therapy with chlorothiazide.

THE EFFECTS OF ADMINISTRATION OF URICOSURIC DRUGS TO PATIENTS ON CONTINUOUS CHLOROTHIAZIDE THERAPY

The following studies were undertaken to investigate some of the changes that occurred in patients on chlorothiazide therapy in response to the administration of various uricosuric agents.

CASE 1.—A 62-year-old man with arteriosclerotic cardiovascular disease and diabetes was noted to have hyperuricemia while on hydrochlorothiazide therapy. He was started on sulfinpyrazone, with a resultant rapid drop in the serum uric acid level (Fig. 1). When

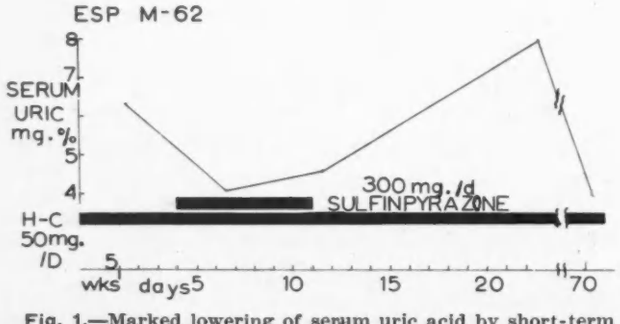


Fig. 1.—Marked lowering of serum uric acid by short-term administration of sulfinpyrazone while on hydrochlorothiazide.

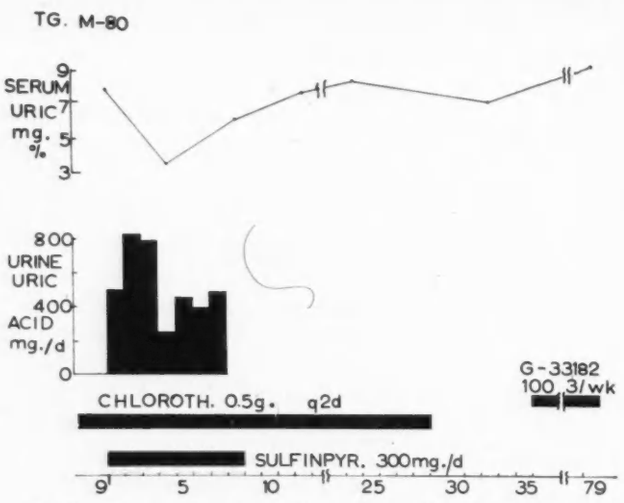


Fig. 2.—Hyperuricemia while on chlorothiazide. Increase in urine uric acid and fall in serum uric acid while on sulfinpyrazone. Note rising serum uric acid while still on uricosuric agent and chlorothiazide. Later chlorthalidane produced hyperuricemia (with only transient lowering of serum uric acid on sulfinpyrazone. Not shown in this chart.)

sulfinpyrazone was discontinued, the uric acid level began to rise; later a spontaneous reduction in the serum uric acid level occurred while the patients remained on hydrochlorothiazide.

CASE 2.—An 80-year-old man with luetic aortitis was discovered to have hyperuricemia while he was taking 0.5 g. of chlorothiazide every second day. The administration of sulfinpyrazone resulted in a fall in his serum uric acid level associated with an increase in urine uric acid (Fig. 2). The serum uric acid began to rise subsequently in spite of continued therapy with sulfinpyrazone. Later the administration of another diuretic agent, G-33192 or chlorthalidone (Hygroton), again resulted in a rise in the serum uric acid level, after which readministration of sulfinpyrazone again produced a temporary fall in the serum uric acid that was not sustained.

CASE 3.—Patient J.P., with hepatic cirrhosis, was noted to have hyperuricemia while on treatment with hydrochlorothiazide. Cessation of hydrochlorothiazide

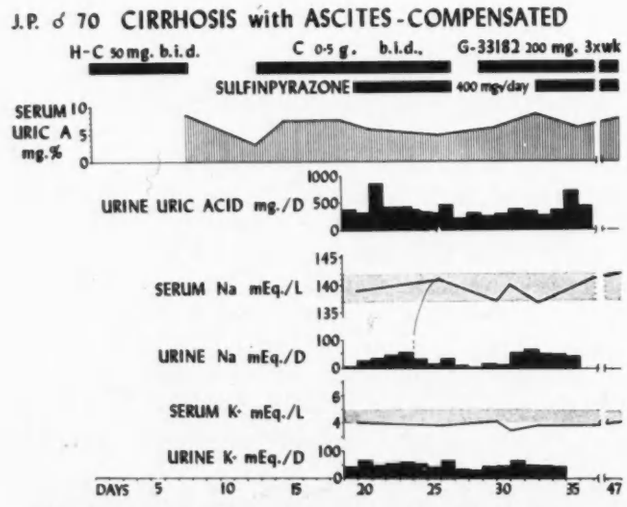


Fig. 3.—Hyperuricemia was noted after administration of hydrochlorothiazide, chlorothiazide and chlorthalidone. Sulfinpyrazone resulted in a transient uricosuric effect with slight transient decrease in serum uric acid levels. The serum sodium level remained within normal limits. Serum potassium was at the lower level of normal throughout.

administration resulted in a fall in the serum uric acid level to normal (Fig. 3). Following this the administration of 0.5 g. of chlorothiazide twice daily again produced a rise in the serum uric acid level which decreased again after administration of sulfinpyrazone. Prescription of another diuretic agent, G-33182 (Hygroton), again resulted in a rise in the serum uric acid. Resumption of sulfinpyrazone therapy resulted in a temporary fall in serum uric acid followed by a subsequent rise, again demonstrating the transient uricosuric effect of these agents while patients remain on hydrochlorothiazide.

CASE 4.—A 66-year-old man with ankylosing spondylitis was noted to have a high serum uric acid which was lowered with probenecid. The introduction of chlorothiazide resulted in a rapid increase of his serum uric acid level from 4.5 to 9.5 mg. % and a decrease in urinary uric acid excretion (Fig. 4). Zoxazolamine was then administered as a uricosuric agent while the patient remained on chlorothiazide, after which the urine uric acid output increased and the serum uric acid level fell. In this instance zoxazolamine (Flexin) appeared to be effective in producing a uricosuric response while the patient remained on chlorothiazide.

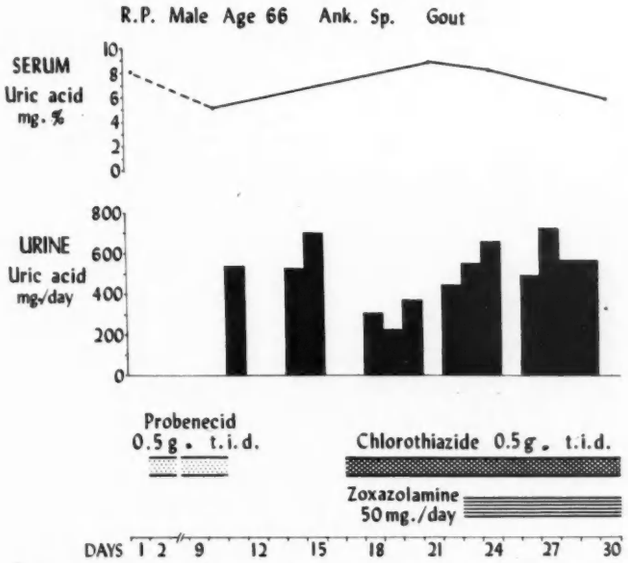


Fig. 4.—Hyperuricemia reduced with probenecid. Uric acid levels rose following introduction of chlorothiazide. Zoxazolamine produced a rise in urine uric acid and a fall in serum uric acid in short (7-day) experiment.

CASE 5.—A 46-year-old patient with congestive cardiac failure, auricular fibrillation, ascites and edema developed an acute attack of gout while on hydrochlorothiazide and mercurial diuretics. Cessation of these drugs resulted in a fall in the serum uric acid level to 6 mg. % (Fig. 5). Sodium and potassium balance studies were then carried out. The re-administration of hydrochlorothiazide in doses of 50 mg. three times a day resulted in an increase in the serum uric acid level to 11 mg. %. Accompanying this there was a transient negative sodium balance. When the serum uric acid was 11 mg. %, zoxazolamine was given in doses of 50 mg. daily. This resulted in only a slight fall in the serum uric acid level from 11 to 9 mg. %; thereafter it remained stationary in spite of an increase in the urine uric acid output. In the last period of the balance study, another attack of gout occurred. During this phase sodium and potassium balance became rapidly negative. In this instance zoxazolamine was ineffective in promoting a lowering of the serum uric acid level.

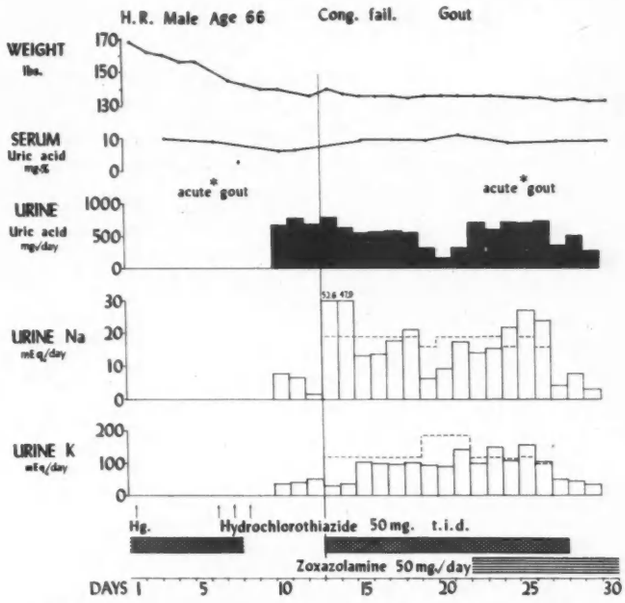


Fig. 5.—H.R., a male, aged 66 (Case 6). Hyperuricemia and acute attack of gout developed while on diuretics. Serum uric acid rose to 11 mg. % on hydrochlorothiazide. Zoxazolamine, 50 mg., was ineffective in lowering the serum uric acid while the patient remained on hydrochlorothiazide. The broken line indicates intake. A negative balance of sodium is above and a positive balance below the line. Note negative Na and K balance at the time of the acute attack of gout on the 24th and 26th days, and also the failure to lower serum uric acid by administration of 180 mEq. of potassium chloride on days 19, 20 and 21.

DISCUSSION

Uricosuric agents therefore had a variable effect in this group of patients. In some cases a sustained lowering of uric acid was achieved while the patient remained on chlorothiazide. In others, the serum uric acid returned to the original high level in spite of continued therapy. This has been observed in patients with and without residual renal dysfunction.

The explanation for these observations may lie in the renal tubular mechanism. As will be noted later, the renal handling of urates may be via both the tubular secretory and reabsorptive mechanisms. Guttman[14] has commented on the paradoxical action of uricosuric agents in that when these drugs are used in low dosage, uric acid excretion is inhibited, while on larger doses urate excretion is enhanced. A similar paradoxical effect has been noted by Healey, Magid and Decker[10] and Demartini[6] with uric-acid-retaining drugs, namely the thiazide derivatives. Small doses of these drugs produce a uricosuric effect while large doses have a urate-retaining action. It is postulated that the effect of uricosuric drugs in low dosage is to block tubular secretion while in high dosage they block tubular reabsorption. With the uric-acid-retaining drugs, low dosage blocks tubular reabsorption and high dosage blocks tubular secretion.

TABLE I.—SUMMARY CHART OF PATIENTS WITH GOUT WHILE ON CHLOROTHIAZIDE.

Case No.	Sex and age	Diagnosis	Dose	Period before onset of signs and symptoms	Serum uric acid mg.%	Therapy	Response	Past history	Diuresis	Remarks and reference
1	F 56	Ess. hypert., osteoarthritis	Chlorothiazide 0.5 g./day	14 days 10 weeks+	9.2* 4.3	Probenecid 1.5 g./day	Slow	Neg.	Neg.	5th proximal interphalangeal joint, x-ray negative.
2	M 73	Arterioscl. ht. dis., Cong. ht. fail.	Chlorothiazide 0.5 g./day	5 months 14 days+	12.4* 6.0	Colchicine. Chlorothiazide discontin.	10 - 16 hours, prompt	Neg.	Neg.	Left ankle and toe.
3	M 80	Arterioscl. ht. dis., Cong. ht. fail., bronch. and emphysema, gout	Chlorothiazide 0.5 g. b.i.d.	7 days	5.8*	Colchicine	14 - 16 hours, prompt	Pos.	Pos.	Right ankle.
4	M 60	Rheum. ht. dis., Cong. ht. fail., diabetes, gout	Chlorothiazide 0.5 g./day	6 months 11 months 13 months	8.6* 7.7 10.3	Phenylbutazone Probenecid Colchicine Probenecid 5 months Chlorothiazide discontinued Probenecid x 1 week	No resp. No resp. Good effect	Pos.	Neg.	Left big toe. Probenecid—transient response. Some renal failure. Persistent hyperuricemia with and without drugs.
5	F 73	Ess. hypert.	Hydrochlorothiazide 50 mg. b.i.d.	13 days 14 days+	6.0* 4.3	Colchicine Probenecid 1.5 g./day	2 courses	Neg.	Neg.	Left ankle. X-ray lesion present.
6	M 66	Arterioscl. ht. dis., Cong. ht. fail., gout	Hydrochlorothiazide 50 mg. b.i.d.	6 days 5 days 9 days+ 7 days+	9.4* 6.1 11.0 10.5	Colchicine Chlorothiazide discontinued Zoxazolamine	Slow No resp.	Pos.	Pos.	Left wrist and ankle, x-ray positive No response to zoxazolamine
7	M 48	Ess. hypert., gout	Chlorothiazide 1.5 g./day 1.5 g./day	5 months 6 days 2 days+ 8 days+ 30 days+	10.3* 12.7 10.4 7.3 9.5	Colchicine Chlorothiazide discontinued Colchicine Probenecid 1 g./day	10 hrs. Rapid	Pos.	Neg.	Transient lowering of uric acid on probenecid. (Healey & Magid[10]) Hydrochlorothiazide. Same response.
8	M	Ess. hypert.	Chlorothiazide 1 g./day Chlorothiazide 1 g./day	3 months 10 days+ 14 days 7 days+	6.8* 3.1 6.4* 4.3	Rest and salicylates Chlorothiazide discontinued Chlorothiazide discontinued	Improvement	Neg.	Neg.	Oren *et al.*[9]
9	M 46	Ess. hypert.	Chlorothiazide 1 g. b.i.d.	6 months 12 days+	6.5* 5.4	Chlorothiazide discontinued	Improvement	Pos.	Neg.	
10	M 40	Recurrent phlebitis	Chlorothiazide 1 g. b.i.d. Chlorothiazide 1 g. b.i.d.	3 days 2 days 7 days+	* 6.2* 3.7	Chlorothiazide discontinued Colchicine Probenecid	Improvement Prompt	Neg.	Pos.	Warshaw[11] Later probenecid and chlorothiazide No treatment.
11	M 48	Rheum. ht. dis., gout	Chlorothiazide 1 g. b.i.d.	3 days ? days	5.8* 3.0	Colchicine Probenecid 2 g./day	Prompt	Pos.	Marked diuresis	
12	M 78	Parkinsonism, ess. hypert.	Chlorothiazide 0.5 g./day Chlorothiazide 0.5 g./day Chlorothiazide 0.25 g./day	3 weeks 6 weeks 8 weeks	10.2* 7.9* 9.9*	Rest and aspirin, chlorothiazide Phenylbutazone and probenecid Colchicine Chlorothiazide discontinued	Improvement	Neg.	Neg.	Neimark *et al.*[12] Transient lowering of uric acid on probenicid. One month later uric acid stones.
13	M 44	Ess. hypert.	Chlorothiazide Hydrochlorothiazide	10 days 1 month 2 months 4 months	9.6* 8.8 5.1 11.0	Chlorothiazide discontinued Probenecid		Neg.	Neg.	Freeman *et al.*[13]
14	M 52	Ess. hypert.	Chlorothiazide 1.5 g./day Hydrochlorothiazide 50 mg. b.i.d.	10 months 5 days 2 weeks	6.3* 7.8 10.8*			Neg.	Neg.	Big toe.

*Attacks of gout

Chlorothiazide inhibits para-aminohippuric acid clearance as well as uric acid clearance. Probenecid inhibits para-aminosalicylic, para-aminohippuric, penicillin and chlorothiazide clearance. Both drugs may act upon the same enzyme systems at the reabsorbing and secretory portion of the tubule. Thus when the patient is on probenecid, chlorothiazide is retained and its level may rise to such a degree that the uric-acid-retaining action of the thiazide may exceed the uric-acid-clearing effect of probenecid.

Studies using high dosage of probenecid and low dosage of chlorothiazide and, vice versa, to assess the role of the relative dosage on uric acid clearance have not as yet been carried out.

PRECIPITATION OF ACUTE GOUT BY CHLOROTHIAZIDE

The precipitation of gout by chlorothiazide, a drug with a broad spectrum of actions, opens up many new avenues in the search for possible disturbances related to the development of acute gout.

Chlorothiazide is believed to result in urate retention by increasing the renal tubular resorption of uric acid. The mechanism of handling of urates by the kidney is still in dispute. Guttman and Yu have shown that renal handling of urates is the same in normal and in gouty subjects and that the tubular resorption of urates increases as the filtered load increases.

While it is established that urate reabsorption does occur, the evidence does not completely rule out the possible existence of a mechanism whereby urates may be secreted by the tubule cells. The evidence for this is that there is a poor correlation between the glomerular filtration, as noted, with the inulin clearance and the urate output, which may be high, normal or low. In other words, the urine urate content shows no correlation with the filtered urate load. The dissociation of the filtered load and urate excretion in the urine is similar to that seen in the handling of potassium, which shows the same anomaly, where a marked tubular secretory component may be present.

The mechanism of the production of acute attacks of gout is unknown. There does appear to be an affinity of cartilage for uric acid but elevated uric acid levels are not invariably associated with overt gout. Gouty arthritis has been precipitated by such diverse factors as trauma, infection, fever, dietary indiscretion, and administration of mercurials, liver extract, penicillin and sulfonamides, thiamine and ergotamine. Now chlorothiazide and its derivatives have been added to the list. The increased urate levels of themselves do not apparently precipitate acute gout. The urate retention that has been reported with chlorothiazide has been noted to occur without change in the blood urea nitrogen[13] or glomerular filtration rate, in patients with and without a diuretic response and without obvious changes in the serum electrolytes.

An alteration in the potassium balance may be a contributing factor in the precipitation of acute gouty attacks. Zumoff and Hellman[18] have shown that the retention of urate by chlorothiazide may be reversed by giving large amounts of potassium chloride. These workers reported that the administration of 180 mEq. of potassium per day to patients on chlorothiazide derivatives resulted in a reversal of the tendency to retain uric acid.

The serum concentration is a poor indication of the actual total body level of potassium. There may be a significant loss of tissue potassium without a change in serum potassium concentration. It is known that the thiazide diuretic agents may produce sodium and potassium loss without weight change. Depletion in these ions may affect the intracellular and extracellular ionic balance and possibly interfere with the enzyme mechanism affecting tubular reabsorption or secretion of urates. These changes may also affect the osmotic and pH levels of the plasma which may be an important factor in maintaining urates in solution in the plasma and at the interfaces where urates may precipitate.

Urates are readily diffusible and are found in all tissues. They are more soluble in an alkaline pH. In the presence of potassium depletion there may be a relative hypokalemic alkalosis in the plasma, while in the tissue cells, and possibly at the cartilage interface, a relative or absolute intracellular acidosis may exist at a pH conducive to the precipitation of urates. A feature which may be common to the urate-precipitating factors noted previously is that they all give rise to an altered or disturbed state of body or a stress of some sort. The solubility, pH or osmotic factors may be altered and gout may be precipitated, in a predisposed person with an elevated urate level.

One may argue that potassium depletion alone cannot be the only factor as patients are often treated with ACTH and cortisone which result in potassium depletion, despite which the gouty manifestations improve. Here a combination of uricosuric and anti-inflammatory action may be present. The fact that ACTH and corticosteroids frequently are associated with gouty exacerbations is in keeping with this concept.

A new look at the effect of osmolar, solubility factors and pH changes upon uric acid metabolism appears to be indicated.

Another interesting association which may have some bearing on the precipitation of gout is that of oxalic acid metabolism.

Patients with primary hyperoxaluria have elevations of uric acid levels higher than are found in patients with renal failure alone. Oxalates like urates are deposited in the soft tissues. Mugler[19] has reported evidence of an impaired oxalic acid metabolism in gout. Patients with gouty diathesis have a reversed blood:urine oxalic acid ratio of 2-3.5:1 compared with the normal of 1:2. Eighty-six per cent of patients with gout and hyperuricemia showed elevated serum oxalic acid levels while only 73% of patients with hyperuricemia alone had elevated oxalic acid levels. Disorders of glycine and purine metabolism are common to both of these disturbances. The authors considered that when hyperoxalemia was present, attacks of gout tended to be aggravated. They also noted that 20% of renal calculi in gouty patients were calcium oxalate stones. It was suggested that hyperoxalemia may in some way account for the fact that some patients with normal serum uric acid levels have attacks of gout. A decreased intake of foods containing oxalic acid may be of value in decreasing the frequency of gouty attacks.

Eight patients described in this report had no previous history of gout nor was there a family history of gouty diathesis. Why did these patients develop gout? More than 80% of patients on thiazide derivatives have elevated serum uric acid levels. Only a small percentage of these appear to develop overt gout. The incidence of gout in the general population is said to be 0.2%.[22] The per-

centage of persons who will develop gout while taking thiazide derivatives is unknown.

Careful study of the histories of the six patients described in this report who were observed by the authors revealed that three had a definite past history of gout and one had a history of a previous attack of "cellulitis" of the dorsum of the hand that was highly suggestive of gout. One woman with a negative history of previous gout had a punched-out radiological lesion in the left ankle. This patient would appear to have had latent gout with a gouty tophus which had never produced symptoms in the past. The two remaining patients, a 56-year-old postmenopausal woman and a 73-year-old man, both had a vague history of articular aches and pains but their joints had never been red or painful or required treatment in the past.

It appears likely that all of these patients may have had gout or latent gout which was exacerbated by therapy with chlorothiazide. To establish this point definitely, it would be necessary to demonstrate that the incidence of gout in patients receiving chlorothiazide is of the same order as the incidence of gout in a comparable sample of the general population.

It is suggested that the diagnosis of latent gout may be facilitated by a provocative test with thiazides for patients complaining of obscure arthralgias who have normal serum uric acid levels and no radiographic changes. On the basis of available data, it might be reasonable to give 2 g. of chlorothiazide per day for a two-week period to provoke a rapid increase in serum uric acid concentration and possibly some derangement in electrolytes which may have some bearing on the precipitation of an acute gouty attack.

It is important to recognize that when drugs are administered with the objective of promoting increased urate excretion in the urine, chlorothiazide and related compounds are contraindicated. Likewise, patients with gout who are well controlled on uricosuric agents may experience an exacerbation if they are given thiazide derivatives which may then result in persistent hyperuricemia in spite of continued treatment with uricosuric agents.

The precipitation of acute gout by chlorothiazide in eight patients with no personal or family history of gout lends support to the concept that there may be an important renal component in the production of hyperuricemia in these patients. Wyngaarden[15] has shown that a large number of patients with a gouty diathesis have an inborn error of metabolism characterized by a tendency to increased formation of uric acid. Gouty patients appear to fall into two groups: those who excrete large amounts of uric acid in the urine (hyperexcretors) and those whose urinary urate excretion is not increased.[20] Recently it has been suggested that among those who do not excrete increased amounts of uric acid in the urine, the production of hyperuricemia may be due to a primary renal factor rather than to an increased rate of uric acid synthesis.[21]

The retention of uric acid and the production of hyperuricemia resulting from the use of chlorothiazide with subsequent precipitation of acute gout lends support to the concept that a renal mechanism for the retention of uric acid may play an important role in the elevation of serum uric acid and in the production of the gouty diathesis.

SUMMARY

Six cases of gout have been reported in patients on thiazide therapy and eight further cases from the literature have been described. There was no previous personal or family history of gouty arthritis in eight of these 14 patients. Patients who develop gout while on thiazide therapy are probably cases of latent gout. Two of the patients in this series were women and 12 were men.

Gouty attacks developed with serum uric acid levels of 5.8 to 12.7 mg. %. Retention of uric acid has been shown to occur with doses of chlorothiazide of 0.5 to 2 g./day, hydrochlorothiazide 50 to 150 mg./day and chlorthalidone (Hygroton) 100 mg. three times a week. Cessation of chlorothiazide resulted in a fall in the serum uric acid levels in all cases but one, a patient with renal disease. Administration of uricosuric agents resulted in a sharp decrease in serum uric acid levels while the patients remained on thiazides, but this effect was not consistently sustained.

Gout is more likely to develop in males on higher doses of thiazides and in those who develop diuresis while on therapy with the diuretic drugs. Increased tubular reabsorption of urates and the possible role of decreased tubular secretion in the hyperuricemia was noted. Disturbances of potassium, oxalic acid, urate solubility, pH and osmolar changes are discussed in relation to the precipitation of acute gout. The "thiazide test" has been proposed as an aid to the diagnosis of latent gout.

REFERENCES

1. Merck Sharp & Dohme Research Laboratories: Chlorothiazide, preclinical evaluation as a saluretic agent, Philadelphia, June 1957.
2. WILKINS, R. W.: *New England J. Med.*, **257**: 1026, 1957.
3. LARAGH, J. H., HEINEMANN, H. O. AND DEMARTINI, F. E.: *J. A. M. A.*, **166**: 145, 1958.
4. CONNOR, T. B. *et al.*: *J. Clin. Invest.*, **38**: 997, 1959 (abstract).
5. YÜ, T. F. AND GUTMAN, A. B.: *Proc. Soc. Exper. Biol. & Med.*, **90**: 542, 1955.
6. DEMARTINI, F. E.: Effect of chlorothiazide on uric acid retention. Presented at Second Pan-American Congress on Rheumatic Diseases, Washington, D.C., June 2-6, 1959. *Bull. Rheumat. Dis.*, **10**: 195, 1959 (abstract).
7. MONROE, K. E. *et al.*: *New England J. Med.*, **261**: 290, 1959.
8. OREN, B. G., RICH, M. AND BELLE, M. S.: *J. A. M. A.*, **168**: 2128, 1958.
9. DOLLERY, C. T., DUNCAN, H. AND SCHUMER, B.: *Brit. M. J.*, **2**: 832, 1960.
10. HEALEY, L. A., MAGID, G. J. AND DECKER, J. L.: *New England J. Med.*, **261**: 1358, 1959.
11. WARSHAW, L. J.: *J. A. M. A.*, **172**: 802, 1960.
12. NAIMARK, A. AND FYLES, T. W.: *Canad. M. A. J.*, **83**: 819, 1960.
13. FREEMAN, R. B., DUNCAN, G. AND GARFIELD, G.: *Metabolism*, **9**: 1107, 1960.
14. GUTMAN, A. B. AND YÜ, T. F.: *Am. J. Med.*, **23**: 600, 1957.
15. WYNGAARDEN, J. B., BLAIR, A. E. AND HILLEY, L.: *J. Clin. Invest.*, **37**: 579, 1958.
16. PETERS, J. P. AND VAN SLYKE, D. D.: Quantitative clinical chemistry. Vol. I, 2nd ed., Williams & Wilkins Company, Baltimore, 1946, p. 949.
17. ZUMOFF, B. AND HELLMAN, L.: *Clin. Res.*, **8**: 35, 1960 (abstract).
18. MUGLER, A.: *Presse méd.*, **67**: 1309, 1959.
19. NUGENT, C. A. AND TYLER, F. H.: *J. Clin. Invest.*, **38**: 1890, 1959.
20. OGRYZLO, M. A.: *Canad. M. A. J.*, **83**: 1326, 1960.
21. STETTEN, D., JR.: *Perspectives Biol. & Med.*, **2**: 185, 1959.
22. ARONOFF, A.: *New England J. Med.*, **262**: 767, 1960.

VIEWPOINTS

ANESTHESIA AND SURGERY FOR JEHOVAH'S WITNESSES

MAX MINUCK, M.D., F.I.C.S. and
RONALD S. LAMBIE, F.A.C.A., F.I.C.S.,*
St. Boniface, Man.

"Tout comprendre rend tres indulgent".
Mme de Stael, 1766-1817

RECENTLY, over a short period of time, the doctors practising at our hospital were called upon to treat several patients of the Jehovah's Witnesses religious order. The problems presented by such patients stimulated a great deal of discussion, discussion which soon pointed up the fact that there exists considerable confusion, emotional bias, intolerance, and ignorance not only with regard to the tenets of the Witnesses' faith but also to the legal and ethical responsibilities involved in their medical treatment. This kind of reaction prompted us to review this universal problem and to try to work out a method of management which would satisfy the moral, ethical and legal position of the physician without interfering with the Witnesses' faith.

The Jehovah's Witness belongs to a religious order that forbids blood transfusions: for he believes that God has literally denied him the right to do so. According to his view, "God has forbidden man to take another's blood in any form into his body. He commanded Noah: 'Flesh with the life thereof, which is the blood thereof, shall ye not eat.' (Genesis 9:34.)" The Witnesses use other references from the Bible to support this belief and these have been well documented in a recent article by Mr. W. Glen How, Q.C.[1b] Since a transfusion of blood is considered to be not merely an act of replacing blood, but a method of intravenous "feeding", they forbid it as an act of eating blood. Should anyone violate this law in any way and do it knowingly and without repentance, he would bring upon himself eternal death. He would deny himself all opportunity for life after death and in addition would be ostracized by his fellow ministers.[1a]

It must be stated in all fairness that this is not the only outcome of receiving blood. If the Jehovah's Witness does not know that he has received blood, either through shock, effect of drugs, or anesthesia, he can in no way be held responsible for this action. Again, if a Jehovah's Witness does allow blood to be transfused, and it is the first offence, he can beg divine forgiveness and forgiveness of God's congregation on earth. Mercy can be extended to him and he need not be disfellowshipped.[2]

In all other respects the Witness' attitudes to life and death are similar to those of any other person and he is not subconsciously or in any other way attempting to attain the "after life" prematurely. He feels that, if he should die as a result of not receiving blood, it is God's will and he will not rebel against God's word by eating forbidden food either by mouth or by vein. We cannot stress too strongly the sincerity with which the Jehovah's Witness believes that he must not violate the Holy Scriptures.

It has been stated that Jehovah's Witnesses is a growing religious order and that we can expect to be faced with this particular situation with ever increasing frequency.[3] Since the Watch Tower Bible and Tract Society, official organ of the Jehovah's Witnesses, does not maintain a membership roll, it was not possible to get exact figures from them except for a statement to the effect that there are 870,000 active ministers in the world. This figure does not reflect the total number of persons regularly attending meetings sponsored by them. The figure for Canada is approximately 38,000.

In an effort to determine the rate of growth of this order in Canada the authors consulted the Dominion Bureau of Statistics. Table I depicts the Jehovah's Witness population in Canada from 1901 until the latest census (1951).

TABLE I.—JEHOVAH'S WITNESS POPULATION IN CANADA

1901	101
1911	938
1921	6689
1931	13,582
1941	7007
1951	34,596

It can be seen that, except for the year 1941, there has been a steady growth of the order. This expansion of this group is significant, for they now are a recognized "minority group" in the statistical analysis of the Canadian population. This stage is attained when a particular group reaches more than 0.2% of the total population of the country.

Table II presents the distribution of the Jehovah's Witness population in Canada in 1951. Col. 1 presents the Jehovah's Witness population distribution. Col. 2 is the total population of the province and territories of Canada and Col. 3 is the ratio of Jehovah's Witnesses to the general population in each province. One can readily see that, although the ratio is much higher in some provinces than others, practitioners everywhere in Canada may be faced with the problem presented by the Jehovah's Witnesses.

*Department of Anesthetics, St. Boniface Hospital, St. Boniface, Man.

TABLE II.—JEHOVAH'S WITNESS POPULATION BY PROVINCE

	Jehovah's Witness	*Total*	*Ratio J.W.: total*
Newfoundland	556	361,416	1:650
Prince Edward Island	111	98,429	1:886
Nova Scotia	1401	624,584	1:458
New Brunswick	522	515,697	1:988
Quebec	1422	4,055,681	1:2853
Ontario	11,485	4,597,542	1:400
Manitoba	3173	776,541	1:243
Saskatchewan	5077	831,728	1:164
Alberta	3493	939,501	1:269
British Columbia	7339	1,165,210	1:158
Yukon	2	9096	1:4548
North West Territories	15	16,004	1:1066
	34,596	14,009,429	1:405

What is the legal and ethical position of the physician in relationship to the adult patient? Dr. T. L. Fisher, Secretary-Treasurer, and Dr. G. W. Armstrong, President, dealt with this very clearly in the fifty-seventh report of the Canadian Medical Protective Association:[4] "The important point is that treatment cannot be given without permission, and doctors should not compromise themselves by giving treatment for which there is no permission, relying on some imagined technicality to protect them if later their action is questioned."

The following examples will show how this particular problem concerning minor children of Jehovah's Witnesses has been dealt with in Canada as well as in other countries.

In November 1958, in Winnipeg, a 14-year-old boy died from hemorrhage following a gunshot wound to the thigh. His parents were members of the Jehovah's Witness faith and refused to allow blood to be administered to the child, despite the fact that several surgeons stated that he would likely die if blood transfusions were not given. On application to the Provincial Government a hearing was held, and then the Provincial Director of Public Welfare asked that the child be placed under the guardianship of the Province. This request was granted and the government, as legal guardians, gave permission for the blood transfusion. These legal postponements, however, delayed the final granting of permission and the child died. As a direct result of this case the Government of Manitoba passed an amendment to the Child Welfare Act in August 1959, enabling blood transfusions to be given promptly to children despite parental objections if, in the opinion of the attending surgeon, the child would die if blood transfusions were withheld.

During the past year an emergency court held in Sudbury Memorial Hospital, Ontario, enabled the 10-year-old son of Jehovah's Witness parents to be given life-saving blood transfusions. Religious objections of the parents were cleared when the magistrate ruled that the patient was a neglected child under the Ontario Child Welfare Act.

In mid-December of 1958 this same problem arose in Toronto, when a child with erythroblastosis fetalis required a transfusion and his parents, Jehovah's Witnesses, refused permission. A court awarded custody of the infant to the Children's Aid Society and the transfusions were begun. There is a likelihood that the precedent set will be followed on future occasions.

In Ann Arbor, Michigan, a child was bleeding internally. Since his parents were Jehovah's Witnesses, it required a court-backed order before blood transfusions could be given.

In Melbourne, Australia, in 1959, a Jehovah's Witness refused to allow a blood transfusion for his two-day-old son suffering from erythroblastosis fetalis. The child died and the father was found guilty of manslaughter.

During October 1960, in Cambridge, England, a magistrate dealt with the case of a newborn baby requiring an exchange transfusion. The father, a Jehovah's Witness, had refused permission for blood transfusion. The court committed the child to the care of officials of the County Council's Children's Department, who authorized the operation. This is apparently the first occasion in England in which this procedure has been used in order to secure legal authority for an operation in opposition to the parents' wishes.[5] It is well known that parents do have a right to accept or reject treatment offered for their child and that a physician has no right to do anything to a child without consent of the parent or guardian. As shown above, only the courts have the power to authorize appropriate treatment under this particular Child Welfare Act pertaining to the region.

Having dealt with the religious and the medico-legal aspects, we shall now list several case histories which reflect the approach to and management of this problem.

1. *Rejection*

Mrs. C., aged 35, was slated for removal of a disc and spinal fusion for chronic backache. When the surgeon discovered that the patient would not accept transfusion, he discharged her from the hospital without surgical intervention.

2. *Blanket Acceptance*

a. Mr. B., aged 74, was admitted to hospital with the diagnosis of benign prostatic hypertrophy. He refused blood. A routine transurethral resection was performed uneventfully.

b. Mrs. C., aged 29, was admitted to hospital with the diagnosis of breast tumour. A simple mastectomy was performed. As a result of intraoperative and postoperative bleeding and oozing, her hemoglobin level, in the immediate postoperative period, dropped to 5 g. She was discharged several weeks later.

c. Mrs. M.C., aged 52, was admitted to the hospital with a diagnosis of carcinoma of the breast. A radical mastectomy was performed, and the patient died the evening of the same day, in spite of blood volume expanders and pressure dressings.

d. Mrs. E.W., aged 29, was admitted to hospital on August 26, with the diagnosis of breast tumour.

Her general condition was good; her hemoglobin level was 12.8 g. A simple mastectomy was performed, with an estimated blood loss of 600 ml. She was returned to the ward in fairly good condition. Extensive bleeding occurred through the Penrose drain and through the pressure dressing. An emergency reopening of the wound was carried out the same evening. Several bleeding points were found and ligated. In the postoperative period her hemoglobin dropped to 5.5 g. on August 30. She slowly recovered and was discharged on September 10.

e. Mrs. E.J., aged 55, was admitted to hospital with a diagnosis of cystocele, rectocele and uterine prolapse. Her general condition was good. Her hemoglobin value was 13.4 g. Under general anesthesia, a Manchester repair and interposition was performed with an estimated blood loss of 800 ml. Two units of Intradex was administered and the patient's immediate postoperative condition was fairly good. Several hours after the operation her condition deteriorated. A hemoglobin estimation made at the time was 7.8 g. Her condition steadily deteriorated and she died at 8:00 a.m. the next morning. Postmortem examination revealed an intra-abdominal hemorrhage of 1200 ml. and in addition a significant amount of free blood was found in the adnexa.

3. *"Slip in Blood"*

During discussions with various anesthetists and surgeons, several stated that they would give blood, without permission, if the need arose. They would either tell the patient that he had received blood in order to save his life, or not tell him on the premise that "What he does not know won't hurt him." One lawyer has been known to tell a panel of physicians that in eight cases he had counselled doctors to give blood transfusions and risk a court action.[6]

None of the above methods of management meets with the authors' approval. Apart from the peculiar problem posed by the Jehovah's Witness, it is certainly not unusual for surgeons and anesthetists to be called upon to treat patients under less than ideal circumstances. The limitations of the patient are dealt with in a calm and objective manner. The physical impairment is assessed and treatment commensurate with the general condition is instituted, usually to the satisfaction of all concerned. For example, in the case of an aged patient with severe myocardial insufficiency and an obstructive rectal carcinoma, surely the surgeon would settle for a palliative colostomy rather than an abdominoperineal resection? Again the patient requiring major surgery, and possessing an unusually rare blood group, would pose a special problem. But so often in the case of the Jehovah's Witness the surgical team becomes emotional, confused and irrational, because the patient's liability is religious rather than physical. Jehovah's Witnesses are not the only religious group which must refuse to accept certain aspects of accepted medical practice on religious grounds. Other groups such as Roman Catholics also must refuse some forms of medical treatment, and we accept their point of view. Similarly the Jehovah's Witness' beliefs should be respected and tolerated.

The problem of management may be dealt with under two main headings, preoperative and intraoperative.

1. *Preoperative*

Concomitant diseases, such as heart disease and pulmonary insufficiency, must be adequately treated as far as possible. Nutritional anemia can be corrected at the rate of 1% per day by oral therapy, and surgery should be postponed until normal levels of hemoglobin have been established. Deficits in proteins may be treated by a high protein diet and aminoacid infusions. Finally, early consultation with the anesthetist is essential in order to allow him to evaluate the patient from an anesthetic point of view, and to select the proper technique.

2. *Intraoperative*

a. Anesthesia. Stated simply, the anesthetic management must concern itself with the agents and techniques that are specifically designed to minimize blood loss. The deliberate reduction of the blood pressure to 80 mm. Hg systolic by the use of drugs or regional techniques may be successfully employed in healthy patients for many procedures. The contraindications to intentional hypotension are: arteriosclerosis, cardiac disease *per se*, cerebrovascular disease, severe hypotension, renal disease, hepatic disease, the extremities of age, severe anemia, hemorrhage, shock, low blood volume, and polycythemia.[7] In the presence of some of the above-mentioned contraindications, e.g. arteriosclerosis, an attenuation of the patient's blood pressure or a technique of modified hypotension may still be useful.

Regional techniques play an important part in minimizing blood loss as well as supplying adequate surgical conditions in prostatic, perineal and vaginal procedures. Rowbotham states that this effect is due to an increased sympathetic vasoconstrictor activity, when the parasympathetic vasodilator fibres are paralyzed and the sympathetic outflow allowed to remain intact.[6]

Hypothermia is another technique which merits our attention. It has become an established adjunct to major cardiovascular surgery. For the Jehovah's Witness undergoing prolonged surgery it is a valuable method for procuring safe hypotension. In addition, it protects the patient by reducing basal oxygen requirements and metabolic demands.[9]

Inhalation anesthetic agents *per se* have been falsely accused of being responsible for increased oozing, but we now understand that the same cause lies in other factors. Since these factors include hypercapnia and hypoxia, great attention must be paid to adequate ventilation or even mild hyperventilation to ensure proper oxygenation and elimination of carbon dioxide.

Canad. M. A. J.
May 27, 1961, vol. 84

Dextran may be used during surgery to restore losses of blood up to 800 ml. Further injection of this colloid is not without greatly increased risks to the patient. Hemodilution with the resultant anemia may lead to peripheral hypoxemia, which can be corrected only by blood transfusions.[10] Work has been done to show that there is sometimes increased oozing with the use of dextran caused by some derangement of the clotting mechanisms. This has been associated with patients who have bleeding times at the upper limits of normal. Experiences in the Korean war have shown that it is unsafe to use dextran when the hematocrit has fallen below 20-25%.[11] It can be fully realized then that synthetic blood-volume-expanders play a useful but limited role in the management of the Jehovah's Witness patient.

An important but little known fact is that immediate autotransfusion is acceptable to the Jehovah's Witness. To strengthen the validity of the statement that autotransfusion is acceptable to the Jehovah's Witness we reproduce the following paragraph from the *Watchtower*, October 15, 1959: "If, however, hemorrhaging should occur at the time of an operation and by some means the blood is immediately channelled back into the body, this would be allowable. The use of some device whereby the blood is diverted and a certain area or organ is temporarily by-passed during surgery would be Biblically permissible, for the blood would be flowing from one's body through the apparatus and right back into the body again. On the other hand, if the blood were stored, even for a brief period of time, this would be a violation of the Scriptures."[12]

The procedure that may be used for collecting blood is as follows. The gauze and compresses are manually extracted and put into bottles containing 20 c.c. of 2% citrate solution or heparin sufficient to prevent coagulation. The remaining blood may be removed from the compresses by immersing them in physiological saline. The blood is then re-infused.[12]

One of us (R.S.L.) has had experience with this procedure in the West Indies. Blood spilled into the abdominal cavity from a ruptured ectopic pregnancy was collected in a sterile two-bottle suction system. Coagulation was prevented by the use of a citrate solution. The blood was then immediately returned to the patient by the intravenous route through the usual filter tubing. No reactions or complications arose from using this particular procedure.

This anesthetic section would not be complete without mention of the correct use of posture.[14] This should be utilized in conjunction with whatever specialized technique is being used, whether it be hypotensive, regional or hypothermia. Whenever possible, the surgical area should be vertically higher than the heart. This postural ischemia is obtained in two ways, good venous drainage and a reduction in the arterial systolic pressure. Gravity induces a gradient in arterial pressure as well as changes in venous drainage. In the elevated parts of the body the systolic blood pressure is reduced by 1 mm. Hg for every 1 cm. elevation. Conversely in dependent regions the pressure is raised by a similar amount.

From the surgical aspect we must stress that extraordinary attention must be paid to gentle handling of tissues and meticulous ligation of all bleeding points, even at the expense of prolonged operating time. Experience has proved that one cannot rely on packs to control postoperative bleeding (*vide supra* Cases 2c and 2d). It is obvious that the surgeon should be prepared to modify his surgery during the procedure if the patient's blood loss and general condition should warrant it.

What can we do for the patient who is a Jehovah's Witness and requires emergency treatment for a hemorrhage catastrophe? The limitation of blood volume expanders has been discussed. Active bleeding must be quickly controlled. If feasible, the bleeding points are tied off, but in conditions such as gastric and para-esophageal hemorrhage, one may resort to the use of circulating cold water through the stomach in the former,[15] and pressure hemostasis, using a Sengstaken-Blakemore tube, in the latter. Other methods of resuscitation will include elevation or bandaging of the four extremities, and the liberal use of oxygen. It has been shown that generalized hypothermia is an important adjunct in the supportive treatment of the exsanguinated patient and should be seriously considered in every patient who is in severe shock following hemorrhage from trauma.[16]

SUMMARY

Our experience has revealed that a great deal of intolerance exists towards members of the Jehovah's Witness order. This is particularly evident when physicians are confronted with them as patients and when the administration of blood is the important part of the management of their condition. An irrational, intolerant, and confused aura surrounds the participants, especially when children are involved.

The medicolegal position is inflexible. There must be permission for treatment; no permission — no treatment. Furthermore, a parent has the right to reject or accept treatment for his child. Should the physician feel that the child will die without blood transfusion, and should he feel morally justified, he can appeal to the government.

When a physician is confronted with an adult patient who refuses blood transfusions, he should accept responsibility for treating him subject to the limitations imposed upon him by the sincere religious beliefs of the patient. A Jehovah's Witness presents no different problem than does the patient in whom ideal surgical treatment is impractical, on account of concomitant physical disease or extreme age.

In the preoperative management of the patient for elective surgery, extraordinary care must be taken to see that he is in optimum condition. Early consultation with the anesthetist is essential to allow him to evaluate the patient and to select the proper technique.

The intraoperative management is concerned with agents and techniques that are designed to minimize blood loss. Induced and modified hypotension, regional techniques, hypothermia, posture, and meticulous attention to proper oxygenation and elimination of carbon dioxide are techniques available to the anesthetist. The use and limitation of blood substitutes have been discussed. In all cases where it is anticipated that large losses of blood will be encountered, the surgical team should collect the blood for immediate re-infusion.[13] This is acceptable to the Jehovah's Witness. The surgeon should meticulously ligate all bleeding points, for experience has proven that he cannot rely on packs to control postoperative bleeding. In emergencies all bleeding points must be quickly controlled where feasible. Other aids may be used, such as localized cooling for gastric hemorrhage and pressure control with the Sengstaken-Blakemore tube for para-esophageal hemorrhage. Other methods of resuscitation are elevation of the extremities and the liberal use of oxygen. Generalized hypothermia is an important adjunct to the treatment of the exsanguinated patient.

Our objective in preparing this paper has been to develop a positive philosophy towards the Jehovah's Witness, and to outline his surgical and anesthetic management. This philosophy will satisfy the legal, ethical and, above all, the moral tenets of the physician, and will not encroach upon the religious beliefs of the Jehovah's Witness.

The medical management of the Jehovah's Witness may be summarized thus: (1) tolerance of his religious beliefs; (2) careful preoperative assessment; (3) postponement of elective surgery if possible; (4) specialized anesthetic techniques; (5) autotransfusions and modified surgery.

REFERENCES

1a. *Awake*, **39**: 21, 1958.
1b. HOW, W. G.: *Canadian Doctor*, **26**: 35, December 1960.
2. *Watchtower*, **82**: 64, 1961.
3. FITTS, W. T., JR. AND ORLOFF, M. J.: *Surg. Gynec. & Obst.*, **108**: 502, April 1959.
4. The Canadian Medical Protective Association: 57th annual report, June 1958.
5. Medicine and the law: *Lancet*, **2**: 976, 1960.
6. Foreign Letters, Canada: *J. A. M. A.*, **169**: 1358, 1959.
7. LITTLE, D. M., JR.: *Anesthesiology*, **16**: 320, 1955.
8. ROWBOTHAM, S.: *Anaesthesia*, **1**: 70, 1946.
9. ALBERT, S. N. *et al.*: *Anesth. & Analg.*, **35**: 570, 1956.
10. THORSEN, G.: *Surg. Gynec. & Obst.*, **109**: 43, 1959.
11. AMSPACHER, W. H. AND CURRERI, A. R.: *A.M.A. Arch. Surg.*, **66**: 730, 1953.
12. *Watchtower*, **80**: 640, 1959.
13. TEZELLI, S.: *J. Internat. Coll. Surgeons*, **23**: 582, 1955.
14. ENDERBY, G. E. H.: *Lancet*, **1**: 185, 1954.
15. WANGENSTEEN, O. H. *et al.*: *J. A. M. A.*, **169**: 1601, 1959.
16. POSTEL, A. H., REID, L. C. AND HINTON, J. W.: *Ann. Surg.*, **145**: 311, 1957.

SPECIAL ARTICLE

PROBLEMS INVOLVED IN DISCHARGING THE "CHRONIC SICK" PATIENT FROM HOSPITAL

J. R. D. BAYNE, M.D.,*
Ste. Anne de Bellevue, Que.

IT IS well known that the proportion of people over the age of 60 in the populations of countries of the western world is increasing. This has been achieved largely by control of the high infant and young adult mortality rate that was formerly prevalent. However, the survival of more people into late middle and old age has resulted in an increase in the incidence of chronic illness. The bulk of cases of chronic illness is found in the middle age group,[1] but the proportion of cases in each age group increases with age. Further medical advances can be expected to prolong life expectancy, with further increases in chronic illness, and also to prolong the lives of those already afflicted. It should be clearly recognized that chronic illness does not necessarily cause disability or crippling,[2] but with advancing age of an individual it is increasingly likely to do so. Quite obviously a matter of major concern for the medical profession now and in the future is the treatment of chronic disease and the prevention of disability.

Although the general hospital might be expected to undertake the care of those people with chronic disabling disease who may require such care and often present particularly difficult problems, in fact such cases tend to be sent to custodial accommodation with inadequate facilities.[3] In Canada it is to be expected that the Hospital Insurance and Diagnostic Services Act will result in increasing numbers of people with chronic disease seeking admission to hospital.

There is a marked tendency for such patients to remain in hospital when they no longer require or can benefit from treatment available there. This is particularly true of elderly patients who, in addition to suffering from one or more chronic conditions, are apt to be faced with economic and social problems inherent in the probability that they are retired, on limited income, widowed, and separated from their children.

On the other hand, it should be noted that only about 3% of all persons aged 65 or over in the United States in 1950 were in institutions of any kind.[4]

Dacso *et al.*[5] found, in a survey of 95 patients in a municipal hospital in New York City, that 90%

*Physician in charge, Gerontology, Ste. Anne's Veterans Hospital, Ste. Anne de Bellevue, Quebec.

had no medically justifiable reason for continued hospital care. He suggested that adequate rehabilitation early in their illness and good medical-social planning might have enabled some of them to return to the community. In a subsequent survey[6] of all New York City municipal hospitals in 1956 it was found that of the patients in all of the "acute" general hospitals, about one-third (31.8%) were discharged home with limited or no activity allowed, and almost one-tenth (9.1%) went home under medical care. Nearly one-tenth (9.7%) were discharged to a nursing home. The survey team that conducted this study[7] estimated the possibility of improvement with adequate rehabilitation and concluded that 17% of all patients in these acute general hospitals needed some degree of rehabilitation whereas less than 1% (0.7%) had completed such a program. It was estimated that of the group discharged to a nursing home, over 30% could, with rehabilitation, have returned home and 25% could have gone to non-medical custodial accommodation. Apart from the obvious benefit to the patient to be enabled to return home or to more independent living, we must also consider that the limited numbers of skilled nursing and other personnel available make it imperative to ensure that these skills are directed to those who really require them.

Clearly it is of the utmost importance to estimate accurately a patient's real needs and potential. It may not always be possible or practical to obtain the opinion of an expert in rehabilitation for all patients with any degree of disability, and often such assessment must depend on the treating physician. To be able to do this each physician must, with the help of the nursing staff, social service department and ancillary services, accurately diagnose the individual needs of each patient. It is not enough to establish a diagnosis based solely on tissue or organ pathology. This identifies the disease but offers no information about the person, his disability or potential for independent living. On the basis of such a diagnosis a hopeless prognosis is sometimes given when in fact the person may still have considerable amounts of time and ability remaining to him.

In some cases a very active program of rehabilitation is required, directed by special teams. In many instances, however, the patient requires a less ambitious scheme. In order to feed himself he may require a spoon attached to a small plastic splint or strapped on his forearm; a one-handed or hemiplegic patient can use a special knife with prongs at the end like a fork. Even patients who tend to spill food can manage if they are given a bib and are propped up at a table, and they derive much satisfaction from feeding themselves. A person who has stiff or painful joints cannot get up if he is put in a low chair and is better in a firm fairly high one. He also can get in and out of bed better if the bed is neither too high nor too low; in most cases it should be about the same height as his chair. Dressing in conventional clothing, even in hospital, often boosts morale but the handicapped person may need loose-fitting clothes, a dress buttoning down the front, shoes fastening with a clasp instead of laces and a long-handled shoe-horn. By having the patient dress himself at least once while in hospital the physician can learn if this will become a problem at home.

A sick elderly person may be incontinent of urine when admitted to hospital, especially since he is often confined to bed with the bedsides raised. If an indwelling catheter is inserted and left in place for some time it may be difficult to achieve continence again. The catheter is a problem for an elderly person, or those attending him, to manage at home. It should be inserted only when absolutely indicated and should be removed early. A high fluid intake is usually desirable for an elderly person but may result in nocturnal frequency if a catheter has not been inserted. Fluids should be taken early in the day and restricted at night to reduce this problem. However, in patients who have lost urinary concentrating ability the fluid load is excreted over a long period and frequency is unavoidable. A receptacle should be readily available in such cases, and if the patient is forgetful he should be reminded to use it regularly and perhaps awakened once at night to do this. Incontinence may often be prevented without resort to a catheter.

These few examples illustrate the approach to the patient's problems that may make the difference between the possibility of his returning home or going to an institution. The specific need can be known only if the treating physician requests that his patient be as independent as possible while he is in hospital. The charge nurse must know what functions are essential for the patient prior to his discharge, and what measures the family must take to preserve maximum independence.

In addition to suffering from chronic illness the elderly person is often subject to conflicts raised by his dependency on others, feelings of inadequacy in himself and awareness of the strain on family relationships and financial insecurity so caused. Such patients should be seen by a medical social worker soon after admission, for help with these problems. Planning for discharge should start when the patient is admitted to hospital so that the social worker has time to work with the family to facilitate the patient's return to his home or transfer to other accommodation if this is needed. In discussing the patient's needs with the family, the social worker must know exactly what these needs are; otherwise fear or pessimism may prevent the family from accepting the responsibility of caring for someone they genuinely love. In some instances it may be that hospital admission terminated a long period of intolerable hostility between the patient and his family, and discharge to other accommodation may be preferable. Often the family will not reveal these factors until the

moment of discharge unless such information is elicited by interviews with a skilled case worker. In finding other accommodation the social worker must know if the patient could live in a private (foster) home, if he can climb stairs, if he requires supervision, if he can only get about in a wheel chair and what medications and follow-up care will be needed. This information must be accurate, practical and simple to understand.

The treating physician must have the answers to the following questions before discharging the patient from hospital:

1. Is the patient independent as far as his personal needs are concerned, and, if not, what exactly must be done for him?

2. Can the patient walk safely alone in the house only, or everywhere including on stairs?

3. Are the diet and medications as few and as simple as possible and does the family or other institution understand them?

4. Do the patient, family or others providing care know what to expect in the course of the disease and what to do in an emergency?

5. What follow-up care is needed, and have the patient and family been reassured that this is arranged?

6. In the event of deterioration, can the patient and family be assured that return to hospital or suitable institution will be arranged?

Unless care is taken to meet these requirements, it is probable that the patient will be reluctant to leave hospital and, if discharged, will soon return, since many of his problems remain unresolved, or he will require transfer to a nursing home where he will receive more skilled care and attention than he really needs or wants.

The following case histories illustrate some of the foregoing principles. The patients were treated at Ste. Anne's Veterans Hospital and were discharged back into their communities. Although this institution is not a general hospital but is devoted to the treatment of long-term illness, the principles involved can be applied to most men or women with chronic disabling disease at any age. A description of the treatment program and of Ste. Anne's Hospital has recently been published[8] but may be briefly reiterated. Ste. Anne's Hospital is a long-stay treatment unit accepting patients from the Queen Mary Veterans Hospital (Q.M.V.H.) in Montreal. It is located at Ste. Anne de Bellevue, 20 miles from the city, in a suburban semi-rural environment. There is a mental infirmary wing for treatment of veterans with psychoses, and a pulmonary disease division for treatment of those with chest disease including tuberculosis. The total bed capacity is just over 1000. The hospital is equipped with laboratory, x-ray facilities, physiotherapy, occupational therapy, arts and crafts and social services departments in addition to a dietary service and veterans' welfare services.

CASE 1.—H.H. was 80 years of age when admitted to the Q.M.V.H. in February 1959 because of hematuria of two months' duration. Investigation revealed a transitional cell carcinoma of the bladder which was treated by implantation of radon seeds. He was a veteran of the South African War and World War I and since that time had had a tremor of the head and right arm of Parkinsonian type, for which he received a pension. In 1937 he had a prostatectomy and in 1938 he was treated for urinary frequency and hematuria. Again in 1944 he had urinary frequency and in 1952, acute cystitis. Since 1954 he had had intermittent claudication of the left leg.

His social history revealed that the patient's wife, aged 75 years, had recently been admitted to a nursing home with a "stroke" and mental deterioration. His son was married, with five children, and lived in Montreal. The veteran had decided to give up his house outside Montreal. His son was willing to accept him in his home but his daughter-in-law was disturbed by the effect the patient's disease might have on her children. It was explained to the patient that he must accept transfer to Ste. Anne's Hospital and this was carried out on March 20, 1959. However, when assessed at that institution he was found to have no symptoms, to be independent as to his personal needs and to have a pleasant personality. A social worker interviewed the daughter-in-law and discussed the problem with her. She agreed to accept the patient into her home.

Follow-up on January 19, 1961, revealed that the veteran lived in his son's home for 18 months and managed very well, reporting regularly to the urology clinic. However, he wished to return to his own house outside the city to be near his old friends and did so on November 1, 1960. His son was not satisfied with the care his mother was receiving in the nursing home, and he and his wife took her to their home when the veteran left. She has improved and no longer requires visiting nurse service although she still must be fed and taken to toilet. The veteran visits them frequently.

In this case the daughter-in-law had been told the nature of the disease but had not understood that the patient was independent and clean in his personal habits. When this was explained and she was told that if symptoms did occur the patient could at once return to hospital, she agreed to accept him in her home. He has remained independent and active for almost two years and the family has even been able to go on to accept the mother back into the home.

CASE 2.—H.J.N. was born in 1890. He had diabetes mellitus for 20 years and took insulin for some years until January 1959, when he was admitted to the Royal Victoria Hospital, Montreal, with gangrene of the left foot. A mid-thigh amputation was performed and he was discharged to his home. His wife could not manage him and in March 1959 he was admitted to Q.M.V.H. He was treated by diet and D.B.I.® Physiotherapy was started but he appeared mentally somewhat confused. He was transferred to Ste. Anne's Hospital in July 1959 for further care.

His progress was slow and somewhat hindered by a degree of contracture in the left hip, but by November 1959 he was walking with an artificial leg and a cane

and could manage stairs. He had worked as a chauffeur for forty years and he paid for his hospital care and prosthesis out of his savings. He was married but had no children. His wife reported to the social worker that in recent months he had become impatient, stubborn and irascible. She had had difficulty in persuading him to follow his diet. She also stated that she had high blood pressure herself and felt unable to care for him. As he became more independent and spoke of returning home, she became more anxious and reported that although he was improving he was still repetitive in his speech. She repeatedly stressed that she was under medical treatment and was not well herself. She continued to visit the patient regularly and it was apparent that there was a bond of affection between them. The patient said that he did not want to be a burden to her.

After repeated interviews with the social worker and frequent walks with her husband in the hospital corridors and grounds, the patient's wife gained confidence enough to obtain a house near the hospital and he was discharged in April 1960. Follow-up at the hospital was easily arranged.

This case illustrates the necessity of continuing rehabilitation as long as the patient makes progress and certainly not to decide against such a program on the basis of the patient's age alone. It also shows how adequate support can enable a worried, elderly, frail wife to accept her husband of whom she is genuinely fond into her home when he is ready to be discharged from hospital care.

CASE 3.—S.B. was born January 2, 1895, in New York State and emigrated to Canada as a child. He served in the army in World War I. He was well until 1958 when he experienced sudden severe headache with weakness lasting three to four days and accompanied by inability to read. This gradually improved and he was not admitted to hospital. On April 2, 1959, he had another severe headache and convulsion. He was admitted to Q.M.V.H. in semicoma. Physical examination showed a complete left and partial right ophthalmoplegia with left ptosis. The left side of his face was weak and he could not swallow. There was incoordination of the extremities, most marked on the left. Reflexes were increased on the left and there was a Babinski response on the right. The neurologist believed that he had a thrombosis or embolus of the basilar artery. A lumbar puncture revealed xanthochromic spinal fluid and anticoagulants were not given. The patient also had pyuria and a chest infection.

He was transferred to Ste. Anne's Hospital on May 26, 1959, by which time he could speak but could not swallow. He was disoriented, emotionally labile and completely dependent in regard to the activities of daily living. He had to be fed and required an indwelling catheter. By November 1959 he was able partly to dress and feed himself. His incoordination made him unable to stand and a wheel chair was ordered for him. By April 1960 he was able to feed himself an ordinary diet, could dress himself, get in and out of bed and a wheel chair alone, and carry on a reasoned conversation.

He was married with five adult children, four of whom were married and only one of whom lived in the area. His wife was well and interested in his discharge although fearful. She was interviewed by the medical staff and was shown that her husband was really independent as far as his personal needs were concerned. A trial visit to the home of a married daughter was arranged and was successful. The patient was discharged to his home, which was a ground-floor apartment in a town about 30 miles from Montreal. The local family doctor was sent a summary of the case and asked to visit the patient to acquaint himself with his present status so that he could provide care as needed.

This case illustrates the possibility of treating successfully even such a severely afflicted person and of successfully discharging to his home a person who requires a wheel chair to get about.

CASE 4.—J.H.B. was born in 1896. He served with the army in France in 1918. He was found to have pulmonary tuberculosis in 1924 and was treated. In 1931 he required admission to the Provincial Hospital in New Brunswick for schizophrenia. Fibrotic pulmonary tuberculosis was noted at that time. In April 1949 he was transferred to the mental infirmary of Ste. Anne's Hospital. He participated in occupational therapy programs but was found to be withdrawn and disoriented and to have hallucinations. Frequent chest radiographs were taken and he was treated with dihydrostreptomycin and para-aminosalicylic acid from February 9 to April 15, 1951. Subsequent radiographs showed no new pulmonary disease although he had several attacks of pneumonia which responded to the usual antibiotics. In 1954 he was transferred to the general medical service and by June 1959 it was felt that he could be discharged to a foster (boarding) home.

Through the local Department of Veterans Affairs social service department the patient's sisters in New Brunswick were contacted but they were not interested in, or capable of, accepting him. They had no objection to his placement in a foster home. The patient was taken to visit the selected home and lived there for two weeks before being asked if he wished to remain. This particular home provided a very protected, comfortable atmosphere where two other veterans had previously been placed and were cared for by an elderly active widow. The patient continues to be followed up from hospital. He has become more communicative, plays cards, watches television, and remains in satisfactory physical health. His funds are controlled by the Department of Veterans Affairs but the "foster mother" is provided with an allowance to purchase clothing and other requirements for the patient.

This case illustrates the possibility of discharging a patient who has hallucinations (he still sees little men beside him and shares some of his food with them) but is not dangerous, provided his new environment will benefit him more than institutional living.

CASE 5.—M.H. was born in Scotland in 1877, one of six children. The family emigrated to Canada in 1885. He served in World War I, sustaining an injury which he said prevented him from working and he was

granted War Veterans Allowance in 1935 at the age of 58 years.

He never married and lived in the same rooming house in Montreal for 30 years. In 1957 he was admitted to Q.M.V.H. with malnutrition, deafness, bilateral cataracts and an old dislocation of the head of the left humerus. He gained weight on an adequate diet and was transferred for domiciliary care to Senneville Lodge, D.V.A. After three months he requested discharge to return to his former lodging house. Shortly thereafter the landlady died and the patient moved but managed poorly and was readmitted to Q.M.V.H. in an emaciated state in September 1958. He gained weight, from 75 to 94 lb., and was later transferred to Ste. Anne's Hospital. He did not gain further weight but tests for malabsorption, and radiological studies of the intestinal tract were negative. Cataract extraction was considered inadvisable because of his poor general physical state. As he did not enjoy institutional living, discharge to a foster home was offered.

In May 1960 his niece unexpectedly appeared, not having seen her uncle for 10 years, and proposed taking him to live with her. Social service investigation revealed that she had recently arrived from the Maritimes, had no resources and was planning to live on the patient's slender income from his War Veterans' Allowance and old age pension which totalled $90 per month. It was apparent that her personality was unstable and that the patient himself did not wish to live with her.

Foster home placement in the home of a local family well known to the social service worker was arranged in August 1960.

Although of independent nature, this patient required supervision and encouragement to eat. His vision was not good and he was sometimes incontinent of urine. The "foster mother" was informed of this and the patient was discharged with a rubber sheet and urinal, and new clothing. His progress was followed up carefully and the "foster mother" frequently contacted the social service department for further advice. She was able to control his elimination problems successfully. However, his niece, of whom he is somewhat fearful, has continued her attempts to interfere despite the patient's lack of interest in her.

This case illustrates the ability to place a frail man with dependency needs in a protective home in spite of his unsure urinary control. It also shows the important protective role that may be required of a social service department to guard a patient from unsuitable plans made by relatives who are emotionally unstable or who have ulterior motives.

SUMMARY

The incidence of chronic illness increases with age although the great majority of elderly persons are still able to lead independent, active lives. When admission to hospital is required for such persons, the complexity of the problems to be faced before discharge tends to prolong their stay in hospital after medical treatment is concluded. Some of these problems are analyzed and an approach to their solution is suggested. Five case histories are presented to illustrate this approach.

REFERENCES

1. PERROTT, G. ST.J. *et al.*: Illness and health services in an aging population, Public Health Service Publication No. 170, Federal Security Agency, United States Public Health Service, Washington, D.C., 1952, p. 3.
2. CHERKASKY, M.: *M. Clin. North America*, **37**: 631, 1953.
3. *Idem*: *Ibid.*, **37**: 1953.
4. SPIEGELMAN, M.: Ensuring medical care for the aged, Richard D. Irwin Inc., Homewood, Ill., 1960, p. 92.
5. DACSO, M. M. *et al.*: Survey of 95 custodial patients in a municipal hospital, Rehabilitation Monograph 7, New York University—Bellevue Medical Center, New York, 1954.
6. RUSK, H. *et al.*: Hospital patient survey, The New York Foundation, New York, 1956, p. 88.
7. *Idem*: *Ibid.*, p. 126.
8. BAYNE, J. R. D.: *M. Serv. J. Canada*, **16**: 728, 1960.

Canad. M. A. J.
May 27, 1961, vol. 84

MISCELLANY

MEDICAL ETHICS – FAITH, FOSSIL OR WAY OF LIFE?*

M. ETZIONY, M.D.,† *Montreal*

MOST writings on medical ethics consider, quite naturally and rightly so, the patient-physician relationship. However, very little attention has been devoted to the confraternal aspect, both historically and in practice. In our present era, all aspects of medical ethics have been largely neglected, except in their circumstantial "public relations" frame of reference. It is this confraternal aspect which has become most sadly forsaken and which I am to emphasize in this paper.

What is medical ethics? One would probably be right if, in speaking of medical ethics in broad terms, one placed the prime emphasis on the idealistic aspect, with due regard at the same time to the justified and acceptable hedonistic interests of the physician. Thus our working definition should therefore be that medical ethics comprises the total conduct of the physician with due regard to the nature of his profession, as well as his personal life, material and spiritual.

The problems and precepts of medical ethics go back to antiquity. In the laws of Hammurabi, King of Babylon (circa 2200 B.C.), we find the earliest extant medical code.[1] The principle of retaliation or recompense, *lex talionis*, was exercised in ancient Hebrew, Greek, Roman and Germanic laws. The Menu code of the Hindus places a high standard of character upon the physician; failure to meet it meant loss of the right to practice. The Magna Charta of medical ethics in our civilization, to this day, has been the Oath, traditionally ascribed to Hippocrates of Cos, written anywhere between the 6th century B.C. and the 1st century A.D. This is not the occasion to go into the controversy regarding authenticity of authorship, time of composition, ideal-humanistic (φιλανθρωπια) or purely professional (τεχνη) intent of its author. Important to us is the indelible impact it has had upon the shaping-up of medical ethics throughout the ages.

The early medieval ethics and etiquette (about 400-1100 A.D.) show a blend of Graeco-Judaeo-Christian idealism. But later, as MacKinney[2] so thoroughly and admirably points out by way of textual illustrations, "For the most part professional cleverness overshadows Hippocratic and Christian idealism. This new secular emphasis, often designated nowadays as modern-mindedness, . . . evolved out of earlier practices, during the late medieval era of rapid urbanization. . . . This trend might be said to mark the despiritualization of the medieval physician." Now the approach is more an "expression of the increasingly secular and materialistic spirit of late medical practice."

One should, for truth's sake, note that physicians throughout the ages, from Hippocrates down to this day, were mindful at all times of their prime duty and obligation to the patient, and that it was the patient and his lay environment that always reminded the physician of the "Oath", but he would be prone to forget the physician's human physical necessities, as soon as the patient got better, and especially when he got worse. Need one at this point draw attention again to the astute observation of the North African, Isaac Israeli (9th to 10th century?)—"Fix the fee of thy patient when his disease is in its ascendency and most severe, for as soon as he is cured he will forget what service thou hast rendered. The more thou demandest for thy service, the higher thou fixest the fee for thy treatment, the greater will they appear in the eyes of the people. Thine art will be looked upon as insignificant by those whom thou treatest for nothing. Do not visit thy patient too often and do not remain with him too long, unless the treatment of the disease demands it, for it is seeing the doctor anew that gives joy to the patient."[3]

Lest it be overlooked it should be remembered that in the A.M.A. code of 1847, the first article on the Duties of Physicians to Their Patients is followed by the article which deals with the Obligation of Patients to Their Physicians. This should serve as a reminder that the idealistic background notwithstanding, medical practice is not a one-way duty or obligation.

This leads to a brief consideration of the most neglected and most controversial subject among physicians today, the confraternal ethics or etiquette. This has become a festering sore nowadays, when medical codes have given way to public relations committees, the latter really being the result of a state of anxiety and defensive feeling, indeed a morbid complex, that has permeated the profession, truly in the spirit of brain-washing, with the resulting "qui s'excuse–s'accuse." Yet everyone would agree that the reputation of the physician must be based on his integrity and knowledge and not on what the patient will say, or on the reaction of any public body.

Take, for example, the question of the patient's changing his physician at any time without any obligation to him. Clinging, or being "faithful" to one's physician, is an archaic, outdated and illogical expectation, argue some "let's-face-it" physicians; it is not a contract, let alone a marriage contract: a patient has a perfect right to change his physician at all times. By the same token, they argue, a patient may decide to change to the consultant who

---

*Presented, in part, before the Osler Society of McGill University, March, 1961.

†Member of the Medical Staff, Jewish General Hospital and Jewish Hospital of Hope, Montreal.

was called in by the physician who had treated the patient for the same illness. However, the medical code of ethics to this day seems to uphold the principle of "I am my brother's keeper", directly and indirectly.

Again, "A wealthy physician should not give advice gratis to the affluent; because it is an injury to his professional brethren, . . . and it is defrauding, in some degree . . . when fees are dispensed with, which might justly be claimed".[4] This idea, incidentally, is close in spirit, if only psychologically, to the ancient Talmudic terse dictum: "A physician for nothing–[i.e. gratis]–is worth nothing."

In the Code of the A.M.A. of 1847[5] this is expressed even more specifically, two paragraphs being particularly relevant: "A physician ought not to take charge of, or prescribe for a patient who has recently been under the care of another member of the faculty, in the same illness, except in cases of sudden emergency, or in consultation with the physician previously in attendance, or when the latter has relinquished the case, or been regularly notified that his services are no longer desired . . . " "When a physician is called to an urgent case, because the family attendant is not at hand, he ought, unless his assistance in consultation be desired, to resign the care of the patient to the latter immediately on his arrival."

This spirit of obligation of one physician to another is clearly and succinctly stated in the Principles of Medical Ethics of the American Medical Association[5]: "A physician should not take charge of, or prescribe for another physician's patient during any given illness (except in an emergency) until the other physician has relinquished the case or has been formally dismissed." And in Section 7, under the heading of "A Colleague's Patient", it is stated that when a physician is asked to see a patient of a colleague . . . "The patient should be returned to the care of the attending physician as soon as possible." Under the title of "Succeeding Another Physician", the Code of the Canadian Medical Association, 1956,[6] puts the matter in just as clear language, though in different phrasing.

Another bone of contention is the question of the term "advertising". In this age of various media of communication, confusion has crept in as to the proper definition of the term. The C.M.A. Code says clearly among others: " . . . Advertising may be very insidious. A physician should not procure, sanction, be associated with or acquiesce in notices which commend his own or any physician's skill, knowledge, services and qualifications." . . . "All opinions on medical subjects which are communicated to the laity by any medium, whether it be a public meeting, the lay press, radio or television, should be presented as from some organized and recognized medical society or association, and not from an individual physician. Such opinions should represent what is the generally accepted opinion of the medical profession." But a physician in a public capacity, e.g., a health officer, may issue statements regarding public health matters.

As regards radio broadcasting, the Canadian Code says, among others: " . . . In any medium of discussion, but especially in radio broadcasting because of its vast range, it is essential that the physician who takes part should avoid methods which tend to his personal professional advantage. . . There is a special claim that physicians of established position and authority should observe these conditions, for their example must necessarily influence the action of their less recognized colleagues. These remarks apply particularly to practising physicians."

Under "Discoveries" the admonition ends with this sentence: " . . . The lay press is not the proper medium for the first announcement of a physician's work or discoveries." Must we then, sometimes, get our first information from lay magazines?

And what of the pediatrician's new concept of maturity and adulthood? On what milk formula ought a 17-year-old to be fed to be still taken care of by this specialist? And how grave must a poliomyelitis epidemic be, to permit a pregnant patient to bring along her husband, parents and in-laws to be inoculated by her obstetrician?

Lastly, the question of a hospital's responsibility to the individual medical practitioner merits consideration. There is no argument about the present-day hospital's role in providing all the necessary care and investigative means for all the sick, wealthy or indigent. But is it not going a little too far when a hospital establishes a clinic for purposes of checkup for the worried business executive, diverting him stealthily away from the practitioner's office?

That this is not merely a hypothetical consideration may be illustrated by the following actual experiences.

A practitioner had a certain patient on his private service. A medical consultant was invited to lend support to an established diagnosis and an obvious line of treatment. After the patient was discharged from the hospital he disappeared and was lost from the practitioner to the consultant. In a similar case, two relatives, patients of a practitioner for years, were referred for consultation to another medical specialist, and disappeared from the former's service to that of the latter. Yet another patient became acutely ill with a prevalent and common illness. For special reasons she insisted on going to a hospital other than that with which her physician has been associated for years. The physician chose with her a hospital and a consultant on the staff of the chosen hospital. The consultant never made any attempt to encourage the return of the patient upon discharge from the hospital to her previous physician.

Many a hospital, too, is oblivious to some measure of sense of duty in regard to the referring physician, who admitted his patient to its public ward. Unless agreed to by the referring physician,

Canad. M. A. J.
May 27, 1961, vol. 84

why should the patient be instructed to report to the hospital clinic for follow-up care?

By the same token, free vaccination of adults for purposes of travelling cannot be excused by claiming it to be a public health measure. The latter can only be accepted as a universal step for the protection of the population at large or in connection with public school and university entrance, but not as an accommodation of the miserly traveller, thus incidentally depriving the practitioner of one of his sources (what a source!) of income.

It should be reiterated here parenthetically but pertinently that I am convinced that a considerable measure of the decline of the overall esteem the public has for the physician today is due to our forsaking of the confraternal philosophy that all physicians are responsible for each other. We have forgotten that medicine is both an art and a science *sui generis* and that we have allowed it to give way and become almost entirely a physicochemical science, without regard to its specific humanistic aspect, hence the resulting "As ye sow, so shall ye reap."

Granted that these and many other matters of medical mores lend themselves to differences of opinion, either because of their complexity, or because of the "change of times," one fact seems obvious: Adherence to a Code is the only reasonable approach. This may be an old code, or if it is obsolete, a new code, but for the good of medical practice and of all concerned, let us not live in anarchy, confusion and misery!

I wish to express my thanks to Dr. H. E. MacDermot for his kind and constructive criticism of this manuscript.

REFERENCES

1. LEAKE, C. D., editor: Percival's medical ethics, Williams & Wilkins Company, Baltimore, Md., 1927.
2. MACKINNEY, L. C.: *Bull. Hist. Med.*, **26**: 1, 1952.
3. FRIEDENWALD, H.: The Jews and Medicine: essays, Vol. I., Johns Hopkins Press, Baltimore, Md., 1944.
4. LEAKE, C. D., editor: Percival's medical ethics, Williams & Wilkins Company, Baltimore, Md., 1927, p. 105.
5. American Medical Association: Principles of medical ethics, revised, American Medical Association, Chicago, Ill., 1954.
6. Canadian Medical Association: Code of ethics, Canadian Medical Association, Toronto, 1956.
7. DAVIDSON, M., editor: Medical ethics, Lloyd-Luke (Medical Books) Ltd., London, 1957.
8. JAKOBOVITS, I.: Jewish medical ethics, Philosophical Library, New York, 1959.
9. ADAMS, F., trans.: The genuine works of Hippocrates, Williams & Wilkins Company, Baltimore, Md., 1939.
10. EDELSTEIN, L.: *Bull. Hist. Med.*, **7**: 236, 1939.
11. JONES, W. H. S.: The doctor's oath: an essay in the history of medicine, University Press, Cambridge, 1924.
12. EDELSTEIN, L.: *Bull. Hist. Med.*, (Supp. I) pp. 1-64, 1943.
13. *Idem*: *Ibid.*, **30**: 391, 1956.
14. RIESMAN, D.: The story of medicine in the middle ages, Paul B. Hoeber, Inc., New York, 1935.
15. KIBRE, P.: *Bull. Hist. Med.*, **18**: 371, 1945.
16. GALDSTON, I., editor: Ministry and medicine in human relations, International Universities Press, Inc., New York, 1955.

CASE REPORTS

ABRUPTIO PLACENTAE IN TWO CONSECUTIVE PREGNANCIES

H. L. CHAPMAN, M.D., *Port Arthur, Ont.*

REPORTS OF CASES of afibrinogenemia or hypofibrinogenemia occurring with abruptio placentae are no longer uncommon in the literature, but a combination recurring in a patient is unusual. A recent report by Fyfe and Grant[1] describes a case similar to the one reported here. Delee[2] first described this hemorrhagic condition associated with abruptio placentae, and Dieckmann[3] noted the markedly reduced level of fibrinogen in patients with hemorrhages associated with premature separation of the placenta. The subject was well reviewed by Murphy, Picot and Thompson[4]; abruptio placenta, dead fetus syndrome, and amniotic fluid emboli were mentioned in this report, and the authors stated that various other causes of hypofibrinogenemia are also known. The most significant hematological change in these patients is defibrination of the blood.

This 21-year-old woman was seen first in January 1957, during her first pregnancy. Her past history is irrelevant. Her condition during pregnancy was good, and her delivery, at term, of a baby weighing 3630 g., on September 4, 1957, was free of complication.

During her second pregnancy she was first examined on November 4, 1958. She stated that she felt well; her weight was 115 lb. and height 5 ft. Hemoglobin value was 12 g.; V.D.R.L., non-reactive; she was group A Rh positive. Her urine was normal. The expected date of confinement was June 4, 1959. Quickening was noted in early January. She was seen frequently prenatally and she felt well during the pregnancy till the day of admission, April 27, 1959. While at a theatre, at 9 p.m. she became ill suddenly, complaining of severe lower abdominal pains. She nearly collapsed on leaving the theatre and was admitted to the Port Arthur General Hospital at 10:15 p.m. On admission examination she showed signs of shock with marked pallor. There was no vaginal bleeding. Pulse rate was 60/min. and blood pressure was 80/50. The uterus was larger than expected and had a board-like rigidity, and there was tenderness in the lower abdomen suprapubically. The pain was steady and persistent. No fetal heart sounds could be heard. Rectal examination showed the cervix in the upper mid-pelvis with no dilatation. Blood examination revealed a white blood

cell count of 23,000 per c.mm. and a hemoglobin value of 9 g. %. The severity of the pain was relieved by intramuscular Nisentil (60 mg.). The diagnosis of abruptio placentae was made; blood was examined for fibrinogen and none was found. A transfusion of stored blood was started, and at the same time fibrinogen was given intravenously. At 11:45 p.m., the cervix was sufficiently dilated for amniotomy and this was performed easily. There was still no vaginal bleeding, and the liquor amnii was not bloody. Her general condition improved somewhat, but her blood pressure kept falling from time to time, being as low as 75 mm. systolic. Labour was slow to start. At 7 a.m., April 28, the cervix began to dilate and progress was rapid. The second stage of labour and delivery were easy and spontaneous with no laceration. The infant was stillborn, weighing 2892 g. The placenta was readily expelled, accompanied by large masses of clots. There was free postpartum bleeding with no appearance of clotting. Fresh blood was being given at this time, and one hour after delivery her condition was much improved and her blood was beginning to clot. Urine excretion was good throughout her delivery. The total amount of blood given was 3500 ml.; 2000 ml. of this was from the blood bank and 1500 ml. was fresh donor blood. The total amount of fibrinogen given was 4.2 g.

The opinion at the time was that the clotting did not appear until the fresh blood was given. Her puerperium was uncomplicated.

An autopsy report on the baby described early maceration beginning in the arms, and congestion of the liver and spleen. There were no congenital abnormalities. The placenta showed no adherent hematoma.

The first examination during her third pregnancy was on April 21, 1960. Her age was now 24 years and she felt quite well. Her weight was 124 lb. and she was in her usual good physical condition with a hemoglobin value of 11.2 g. %, a normal urinalysis and a blood pressure of 110/60 mm. Hg. Her expected date of confinement was October 16, 1960. Quickening was felt in early May. She was quite comfortable and her pregnancy was progressing normally. She was examined frequently, although she lived 200 miles away in a timbering centre. At her last prenatal visit on August 5, 1960, she had no abnormal signs. The fetal heart sounds were well heard. The fundal height by caliper measurement was 21 cm. Her weight was 137 lb., and her blood pressure was 96/50 mm. Hg. There were no signs of toxemia. On September 4, 1960, at 9 a.m., she started to have abdominal pain. She was brought into hospital in an automobile over rough roads, taking five hours for the trip. On admission there were signs of shock and concealed hemorrhage, as with her second pregnancy. No fetal heart sounds were heard. Blood was matched and donors for fresh blood were obtained (since reference to her previous case suggested that she appeared to respond better with fresh blood than with fibrinogen administration).

While fresh blood was being matched, bank blood and dextran were given and her membranes were punctured.

Her blood pressure was 102/60, pulse 100/min., hemoglobin value 9.4 g., and Fibrindex over five minutes. Morphine, grain 1/6, was given. There were no definite signs of labour until about six hours after admission. Cesarean section and/or oxytocic drip were considered, but section was not performed because of her poor state of blood clotting. At midnight a slow drip of Syntocinon in saline was started, but after only a few drops were given it was seen that her reaction was too vigorous for safety and it was promptly discontinued. At this time the uterus was as high as the xiphisternum, causing respiratory discomfort. Her pulse was rapid at 120 per minute. Her blood pressure ranged around 74/40 mm. Hg. Urinary excretion was good.

At 10 p.m. a tube of blood, which had been sent for testing, clotted as soon as it reached the laboratory. Her hemoglobin level fell to 7 g. %. It was difficult to time her labour pains, which were not definite, but by 11:30 p.m. the fetal head presented and she was easily delivered under nitrous oxide and oxygen anesthesia. There was a great amount of retroplacental clot, and the blood expelled with the placenta was estimated at between 4 and 5 litres. The stillborn baby weighed 2240 g. and showed early signs of maceration, as though it had been dead for most of the day. After delivery the patient's hemoglobin value was 6 g. %, but the defibrination was well controlled. The total amount of blood given was 1000 ml. of stored blood and 3500 ml. of fresh blood. No fibrinogen other than that present in the transfused blood was administered.

DISCUSSION

A wide variety of cases of hypofibrinogenemia have been encountered by the author in the past ten years. When donors for fresh blood were not readily available, stored fibrinogen was given, usually with satisfactory results, but the impression was gained that fresh blood is associated with a more rapid response. A recent patient with abruptio placentae developed late homologous serum jaundice after packaged fibrinogen was used. A stock of commercially prepared fibrinogen and a quantity supplied by the Canadian Red Cross Society is kept readily available. Blood donors are usually easily obtained at any hour through the co-operation of the Red Cross Society.

SUMMARY AND CONCLUSIONS

A case of repeated afibrinogenemia in a patient with two consecutive pregnancies terminating with abruptio placentae is reported.

The basis of treatment is to administer fibrinogen, treat the shock and complete the delivery.

Fibrinogen of fresh blood appeared to be as efficient as the commercial product.

Cesarean section is not resorted to if delivery is progressing favourably and defibrination is being corrected.

I would like to thank Dr. G. A. Cram for his assistance with the last case.

REFERENCES

1. FYFE, A. E. AND GRANT, M.: *J. Obst. & Gynaec. Brit. Emp.*, **67**: 649, 1960.
2. DELEE, J. B.: *Am. J. Obst.*, **44**: 785, 1901.
3. DIECKMANN, W. J.: *Ibid.*, **31**: 734, 1936.
4. MURPHY, C. J., JR., PICOT, H. AND THOMPSON, H. G.: *Ibid.*, **72**: 1197, 1956.

Canad. M. A. J.
May 27, 1961, vol. 84

FALSE ANEURYSM IN A TEFLON FEMORO-POPLITEAL BYPASS GRAFT

GEORGE E. MILLER, M.D.* and
GEORGE B. ELLIOTT, M.B., *Calgary, Alta.*

SINCE THE advent of a direct surgical attack on aneurysms and obliterative arterial disease, various prostheses have been used as substitutes for the diseased vessels. Initially, homografts were favoured but latterly these have been used less and less because of the difficulties associated with the setting up and maintenance of an adequate vessel bank. In addition it was found[1, 6, 7] that homografts were susceptible to the same arteriosclerotic changes as the host's vessels.

To circumvent these two major problems a search for a perfect artificial prosthesis was undertaken and various substances such as vinyon N, ivalon, orlon, nylon, dacron and, most recently, teflon, have been used. All but dacron and teflon have been largely discarded for various reasons mainly concerned with poor host tolerance and degenerative changes in the substances themselves, leading to graft failure.[2, 5] The latter two substances seem to avoid most of these pitfalls and in addition are as easy to handle as homografts.[2-4, 7] Neither seemed prone to degenerative changes and both are well tolerated by the host. In addition, teflon is now constructed in a tight weave which allows for minimal blood loss on opening the arterial clamps, thus eliminating the last major objection to the use of artificial prostheses.

We have recently encountered a case in which a knit teflon graft inserted as a femoro-popliteal bypass some 18 months earlier unexpectedly disintegrated sufficiently to allow the formation of a large fusiform aneurysm about its mid-point. This was resected and successfully replaced by a woven teflon graft.

Mr. J.G., an active 64-year-old white farmer, was first seen in January 1959, complaining of intermittent claudication which involved the left leg and limited walking to one block at a slow pace. An aortogram showed mild arteriosclerotic involvement of the aorta and its proximal branches. The left superficial femoral artery was blocked throughout its middle one-third. An excellent run-off was demonstrated, however, and so the defect was bridged by a knit teflon graft ⅜ in. in diameter, extending from the common femoral to the popliteal artery. Upon opening the graft, good pulses were palpable at the ankle. The patient had a normal convalescence and was discharged in 10 days. He was seen in three weeks and again at three months subsequently. On each occasion pulse remained good at the ankle and he had no further complaint.

He was well until the spring of 1960, some 15 months after operation, when he felt a tearing sensation in the mid left thigh while straining to lift a 50-gallon drum of gasoline on his tractor. Moderate pain persisted in the region for the next 48 hours, but was not severe enough to interfere with his spring farm work, and there was no return of claudication.

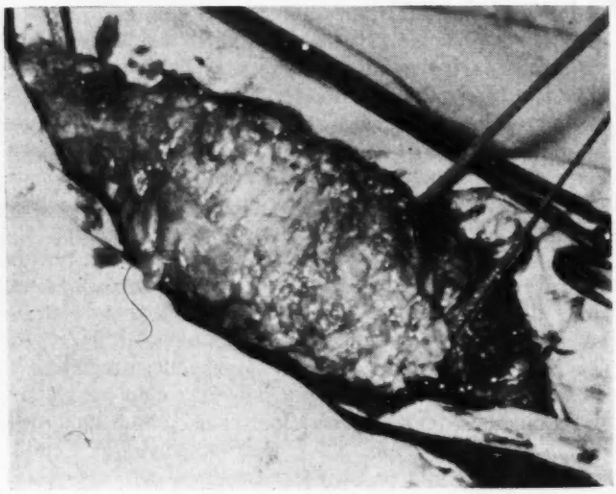


Fig. 1.—The exposed false fusiform aneurysmal sac.

About three weeks after this incident, he noted a walnut-sized pulsatile swelling at the site of his recently noted pain. This expanded slowly over the next three months to the size of a lemon. During a lull in his farm work he returned for examination. The mass was found to lie around the mid-point of the graft. It pulsated, exhibited a murmur on auscultation, was slightly tender and measured 8 in. in length and 3½ in. in width. Good pulsation was present in the graft above and below the mass, and the popliteal, dorsalis pedis and posterior tibial pulses were excellent.

A diagnosis of aneurysm was made and the patient re-admitted to hospital for exploration.

At the second operation the femoral artery was secured above the graft insertion and the graft was secured below the mass, which was then explored. It proved to be a false aneurysm (Figs. 1 and 2).

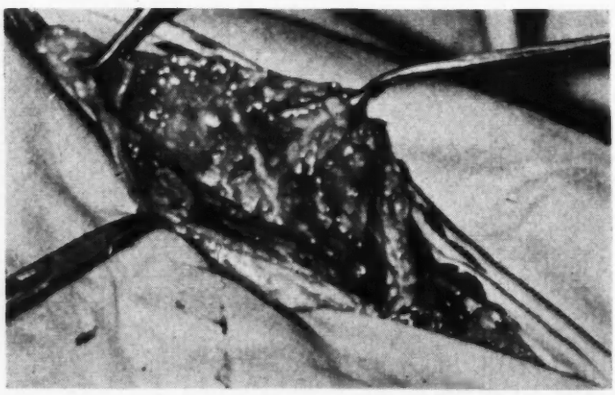


Fig. 2.—The opened false aneurysm shows a smooth lining incorporating the remains of the teflon graft.

The graft above and below this area was very closely invested by the usual fibrous reaction and was unexpanded and of normal calibre. Accordingly, the aneurysmal area was widely excised and the graft was replaced by a new segment of woven teflon prosthesis (Fig. 3). Satisfactory anastomosis was accomplished and after release of the clamps good pulses were again present in the popliteal and distal vessels at the ankle.

*From Department of Surgery, Calgary General Hospital, Calgary, Alberta, and Cardiovascular Department, Calgary Associate Clinic.

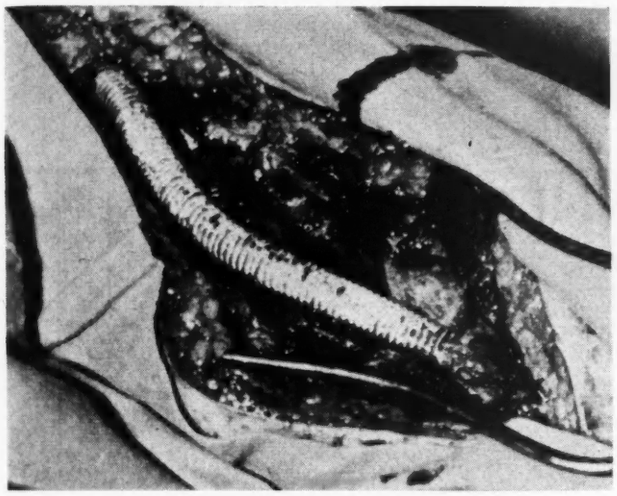


Fig. 3.—A new woven teflon graft replaces the fusiform aneurysm.

Examination of the excised false aneurysm showed a fusiform lumen 3.5 cm. in diameter over a 9 cm. segment. Part of its wall was formed by the old graft, but this had split apart longitudinally in several places. The remainder of the wall was thus formed by collagenous scar tissue with a thin inner lining of laminated organized thrombus. Vascular continuity had been maintained by this expanded fibrous sheath of the host which had enclosed the old graft. No inflammatory reaction to the teflon was detected.

The patient has remained well since his second operation and indeed has supervised the fall harvest.

Discussion

It would appear that the teflon prosthesis had split longitudinally in several places around the circumference of the mid-portion of the graft while the patient was lifting a gasoline container. The dense connective tissue reaction around the prosthesis formed a sheath which maintained the vessel's continuity, but lacked elasticity and tensile strength, and underwent stretching over the subsequent weeks. This allowed the slow formation of a false aneurysm.

It was interesting to find that the sheath of the graft above and below the aneurysm was firmly adherent, allowing one to handle the prosthesis as one would a normal blood vessel.

Splitting of teflon in this case illustrates the great functional strength required in major human arteries and the need for further research to duplicate this in synthetic graft material.

Summary

An instance of longitudinal splitting in a knit teflon femoro-popliteal bypass is reported. It occurred 18 months after insertion for vaso-occlusive disease and ruptured under mechanical stress of heavy lifting. A false fusiform aneurysm formed in the fibrous sheath to the graft. This was excised later and was successfully replaced by a woven teflon graft.

References

1. Keefer, E. B. and Glenn, F.: *S. Forum*, **7**: 328, 1957.
2. Deterling, R. A., Jr.: *Surg. Gynec. & Obst.*, **104**: 227, 1957.
3. Harrison, J. H.: *Am. J. Surg.*, **95**: 16, 1958.
4. Edwards, W. S. and Lyons, C.: *Surg. Gynec. & Obst.*, **107**: 62, 1958.
5. Harrison, J. H.: *Ibid.*, **108**: 433, 1959.
6. Sheranian, L. O., Edwards, J. E., and Kirklin, J. W.: *Ibid.*, **109**: 309, 1959.
7. McKenzie, A. D.: *Am. J. Surg.*, **100**: 176, 1960.

SHORT COMMUNICATION

THE CELL FRAGILITY OF ERYTHROCYTES FROM SCHIZOPHRENIC PATIENTS*

R. HOARE, Ph.D.,† *Brandon, Man.*

Differfnce in cell fragility have been found in erythrocytes obtained from schizophrenic and from non-schizophrenic patients.[1] A review of papers on this subject[2, 3] reveals that the studies did not make use of a method with a minimum of uncontrollable variables such as age, duration of hospital stay, sex and drug regimen. The evidence presented did not seem to be based on a sufficiently controlled experiment for the finding of any significant difference between schizophrenic and non-schizophrenic cells. For this reason, the author has carried out a carefully controlled study on a small group of selected patients and a control group working in the same environment and chosen according to the same criteria.

*From the Brandon Hospital for Mental Diseases, Brandon, Manitoba.
†Box 420, Brandon, Manitoba.

Method

The method used was adapted from that of Hunter[4] in which oxalated venous blood was carefully centrifuged at moderate speed (1500 r.p.m.) for 10 minutes. The supernatant plasma was removed and the packed cells were washed three times with 0.85% sodium chloride, with inversion and centrifugation after each wash. The erythrocytes were finally suspended in 2.0 ml. of Alsever's solution[5] at pH 6.1 and stored at 15° C.[6]

An aliquot (0.05 ml.) of the cell suspension was carefully pipetted, with rinsing, into exactly 10.0 ml. of a saline solution at pH 6.1. A series of 26

saline solutions of strengths ranging from 0.20 g. per 100 ml. to 0.70 g. per 100 ml. (in steps of 0.02 g. per 100 ml.) was prepared. Four tubes were set up for each level of saline used. After the addition of the blood, each tube was inverted three times and allowed to stand exactly one hour at room temperature (25° C.). At the end of the hour the tube was inverted once and centrifuged for 15 minutes at moderate speed (1500 r.p.m.). After centrifugation the absorption of the supernatant saline in each tube was read in a 10-mm. silica cell in a Beckman DU spectrophotometer at 540 mμ. The 100% hemolysis value was obtained by adding 0.05 ml. of cell suspension to 10.0 ml. of 0.1% sodium carbonate solution with inversion, followed by a reading in the Beckman DU spectrophotometer.

Four separate determinations were made for each cell sample at each saline concentration. Schizophrenic and control samples were run concurrently with saline levels and read in a random distribution.

CHOICE OF SUBJECTS

Subjects, both control and schizophrenic, were chosen according to the criteria of Perlin and Lee[7] for the selection of a small group of schizophrenic subjects for biological studies. Restriction of the variables—age, sex, race, length of hospitalization and freedom from overt complicating factors—was applied, as follows:

Age.—The age range 20 to 30 years was chosen. Below 20 years biological patterns with variables characteristic of the adolescent period would be shown. Above 40 years, ageing would be a contributing factor.

Sex.—Male patients and controls were chosen. More biological data are established for males, and certain complex psychophysiological phenomena in females are avoided.

Race.—All patients were white, since the available white schizophrenic group is larger and better characterized.

Length of hospitalization.—The period was between two and 10 years. A maximum of 10 years was chosen in an attempt to limit the more extreme effects of lengthy hospitalization.

Freedom from complicating factors.—All of the patients chosen had not been on any type of treatment or medication for at least one year.

Control or Non-Schizophrenic Subjects

Healthy attendants were used as control subjects who fulfilled the same criteria of age, sex and race as outlined for the schizophrenic patients.

RESULTS

The results for both groups, control and schizophrenic, are shown in Fig. 1. This indicates the usual sigmoid curves obtained by plotting the percentage hemolysis values on the ordinate against saline concentrations on the abscissa.

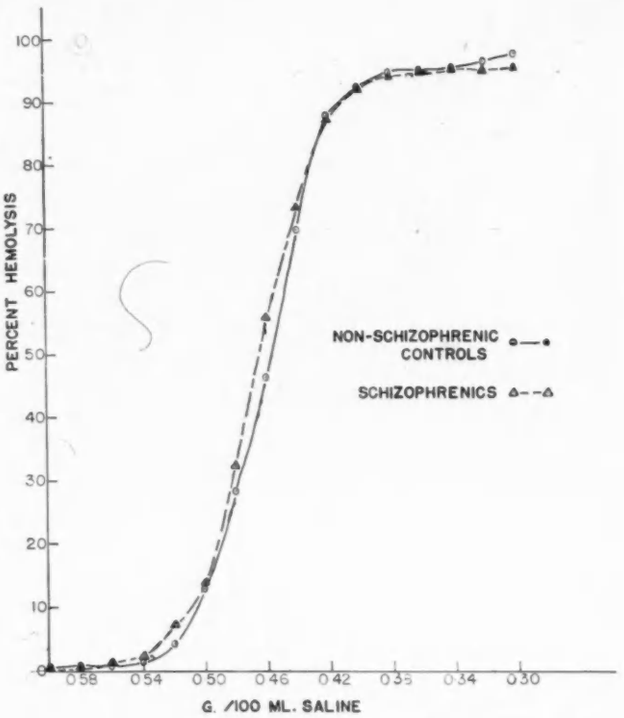


Fig. 1.—Percentage hemolysis of red blood cells from schizophrenic and non-schizophrenic subjects.

To translate this into a straight line relationship, the data were plotted directly on arithmetic probability paper (Codex No. 3227). The straight line portion of this curve, shown in Fig. 2, is then the first differential of the sigmoid curve and gives the probability distribution of the erythrocyte fragility of control and schizophrenic bloods for varying concentrations of salt solution.

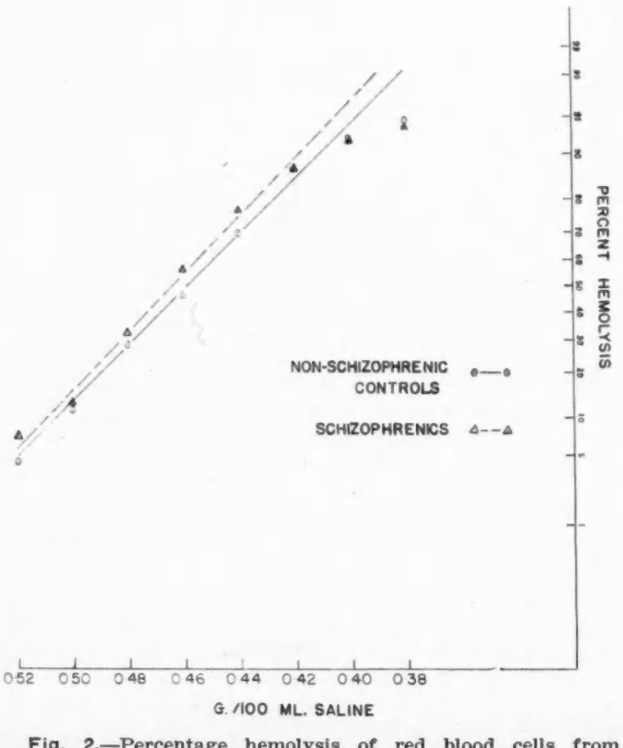


Fig. 2.—Percentage hemolysis of red blood cells from schizophrenic and non-schizophrenic subjects.

TABLE I.—PERCENTAGE HEMOLYSIS OF RED CELLS FROM SCHIZOPHRENIC AND NON-SCHIZOPHRENIC SUBJECTS

		Subjects																						$\frac{8}{\sqrt{n}}$
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	$\overline{X}$	
Schizophrenic	40	95.9	86.6	97.6	90.5	85.8	94.3	94.6	94.7	82.3	92.2	96.8	96.7	92.7	91.2	94.9	96.0	88.8	95.9	90.2	91.7	91.6	91.6	1.2
	42	92.2	83.8	100	93.0	83.7	84.8	88.4	92.6	70.0	81.6	93.6	92.8	85.5	88.3	88.4	91.1	84.1	93.3	81.2	86.9	87.3	85.5	1.5
	44	88.3	79.9	93.6	87.7	76.8	60.4	80.4	88.2	44.4	59.4	89.3	89.1	71.4	65.6	63.0	77.8	69.2	81.9	62.8	74.6	74.1	75.1	2.7
	46	72.4	59.6	86.6	61.8	64.2	44.1	60.1	84.7	26.4	38.5	78.1	80.2	52.9	42.9	38.3	68.1	49.9	75.1	36.6	53.6	56.5	58.6	3.7
	48	47.8	41.4	56.0	20.9	40.7	8.2	32.4	66.9	10.5	22.3	53.6	73.7	24.9	18.4	12.7	44.5	28.3	51.5	18.9	34.0	31.0	35.2	3.9
	50	26.2	17.9	41.6	33.9	20.0	6.2	12.7	46.7	5.0	5.0	22.0	34.5	10.9	8.9	4.8	17.6	12.2	31.1	8.4	16.6	11.9	18.8	2.7
	52	10.6	11.0	29.6	11.4	5.8	2.5	6.6	33.0	1.4	0.8	9.5	17.5	6.9	1.2	1.3	2.8	1.8	16.4	2.6	6.1	8.3	8.9	1.9
Non-schizophrenic	40	88.0	91.5	95.2	89.1	94.1	97.7	95.6	97.1	97.0	96.2	85.1	91.2	96.8	81.5	89.5	89.9	91.2	93.6	89.6	94.1	93.3	92.3	0.9
	42	77.5	79.3	75.9	101	89.4	95.7	91.8	93.2	91.9	92.5	75.5	84.6	91.9	82.6	86.2	87.5	89.0	92.0	86.7	89.3	86.8	88.1	1.4
	44	54.2	71.1	67.4	91.0	86.5	91.4	82.2	83.2	83.7	88.2	60.0	69.6	84.8	66.2	75.1	80.7	73.3	82.3	60.4	80.5	64.2	76.0	2.4
	46	25.4	53.4	32.4	66.1	77.4	80.4	80.8	70.8	65.9	80.7	43.9	47.0	73.1	35.3	58.7	66.6	45.5	63.8	36.7	64.7	36.7	57.4	3.8
	48	21.9	36.9	31.3	49.7	58.0	60.7	64.2	41.2	38.2	65.9	16.5	23.1	39.3	22.1	36.0	46.6	35.1	48.9	21.6	39.4	18.9	38.8	3.3
	50	5.2	13.7	15.4	41.1	36.5	34.8	15.9	23.9	9.2	29.5	8.5	9.4	29.7	4.3	10.9	25.9	20.1	13.0	3.2	21.0	9.5	18.1	2.3
	52	2.4	2.9	7.8	11.3	21.0	13.5	6.0	8.3	1.0	6.7	2.9	4.6	8.2	2.3	4.7	6.5	5.5	4.3	2.8	4.4	4.2	6.3	1.0

The straight line portion of both curves when plotted as the first differential of the sigmoid, on arithmetic probability paper, fell consistently within the range of concentration 0.40 g. per 100 ml. and 0.52 g. per 100 ml. Therefore values within this range were used for a statistical analysis of the results in comparing schizophrenic patients and non-schizophrenic controls. Data obtained in this manner are presented in Table I. Twenty-one schizophrenic patients and 21 non-schizophrenic controls were used in this study.

DISCUSSION

In checking this method used for the determination of erythrocyte fragility, it was found that the stability of the washed cell suspension was low, and that it was only slightly increased by the use of Alsever's solution. That is, the optical density readings in saline solutions tended to decrease with time for the same sample of erythrocytes. All variables such as time of hemolysis, pH, temperature, speed and time of centrifugation were rigidly controlled and produced very consistent results in replicate determinations. These replicates were carried out in a randomized manner in order to remove any personal bias. Hematocrit determinations were all found to be within the range of 40 to 45%, with the exception of two samples which were not used for cell fragility determinations. Since these hematocrits were within the limited range, and all the cell suspensions were made in identical volumes of Alsever's solution, no adjustment was considered necessary in the percentage hemolysis results.

Initial work done with the determination of hemoglobin in the cells for per cent hemolysis calculation and hematocrit correction to give the fragility index showed no advantage in this method over a direct calculation of the percentage hemolysis by means of optical density readings.

STATISTICAL ANALYSIS OF RESULTS

Standard errors for readings from solutions with concentrations from 0.40 to 0.52 g. per 100 ml. saline inclusive varied between 4.0 and 18.2 for the schizophrenic group and between 4.3 and 17.6 for the non-schizophrenic group.

Standard errors of the means varied between 0.9 and 3.9 for the schizophrenic group and 0.9 and 3.8 for the controls. In no instance did the difference between the means exceed one standard error of the difference. For example, for the 0.04 g. per 100 ml. saline, the difference is 0.2. The standard error of this difference is 1.8. For the 0.46 g. per 100 ml. saline, the difference is 1.2, with a standard error of the difference of 5.3.

There is no evidence to indicate a difference between the fragility of the erythrocytes of schizophrenics and controls. There is evidence that between the groups as constituted in this study there is no significant difference in this regard.

CONCLUSIONS

An examination of the basic data showed that if a significant difference did exist between the two groups, this study should have indicated such a difference. A difference of 4 to 12 in the means at different concentrations of saline would be quite possible and would therefore be significant. However, no difference in the means greater than 3.6 was observed.

I wish to acknowledge with thanks the technical assistance of Mr. L. T. McCabe and the valuable advice and assistance of Dr. W. Schlichther, Clinical Director, and Mr. L. Henderson, Research Assistant.

REFERENCES

1. HOFFER, A.: *Dis. Nerv. System*, **20**: 87, 1959.
2. LEACH, B. E. AND HEATH, R. G.: *A.M.A. Arch. Neurol. & Psychiat.*, **76**: 444, 1956.
3. MEGEL, H. AND GORDON, A. S.: *Endocrinology*, **48**: 391, 1951.
4. HUNTER, F. T.: *J. Clin. Invest.*, **19**: 691, 1940.
5. KABAT, J. AND MAYER, M. M.: Experimental immunochemistry, Charles C Thomas, Springfield, Ill., 1948, p. 107.
6. EAGLE, H.: The laboratory diagnosis of syphilis, C. V. Mosby Company, St. Louis, 1937, p. 95.
7. PERLIN, S. AND LEE, A. R.: *Am. J. Psychiat.*, **116**: 231, 1959.

Canad. M. A. J.
May 27, 1961, vol. 84

THE CANADIAN MEDICAL ASSOCIATION
JOURNAL
LE JOURNAL DE
L'ASSOCIATION MÉDICALE CANADIENNE

published weekly by
THE CANADIAN MEDICAL ASSOCIATION
Editor, C.M.A. Publications:
DONALD C. GRAHAM, M.D., F.R.C.P.[C]
Managing Editor: T. C. ROUTLEY, M.D., F.R.C.P.[C]
Associate Editor: GORDON T. DICKINSON, M.D.
Assistant to the Editor: ROBERT L. RANDALL
Editorial Offices: 150 ST. GEORGE ST., TORONTO
(Information regarding contributions and advertising will be found on the second page following the reading material.)

HOSPITAL CASUALTY SERVICES

A SELF-CRITICAL publication by doctors concerning some aspects of the practice of medicine is always of interest to the profession. Such a document is the 135-page booklet entitled "Casualty Services and their Setting", recently published by the Oxford University Press. The study on which this report is based arose out of a colloquium on the future of medical care in Great Britain, sponsored by the Nuffield Provincial Hospital Trust and held at Christ Church, Oxford, in December 1957. Time and again, in debating quite separate issues, serious concern was expressed about the state of casualty services throughout the land. As a result, a seven-man steering committee was appointed in the summer of 1958 to conduct a survey of such hospital services. "Casualty Services and their Setting" is this committee's report.

It begins, appropriately enough, with a summary of the committee's main conclusions and recommendations. Then follows a meticulous account of the methodological techniques employed in the collection and analysis of the data reported. If for no other reason this report might well be taken as a model for future investigations of this type.

The main problems encountered by the committee fell within three groups: (1) serious overcrowding combined with faulty departmental design impending the smooth flow of patients; (2) confusion resulting from difficulties in separating true casualties from "casuals", i.e. ambulatory patients seeking advice concerning trivial complaints; and (3) lack of 24-hour consultant coverage.

Of considerable interest is the committee's observation that the efficiency of a hospital emergency department was directly related to the skill and ability of the nurse in charge who, in many cases, was able to provide a remarkably efficient service in an antiquated building. In contrast, it was noted that some of the newest of the hospitals surveyed, i.e. those constructed after the National Health Service was established, operated the most inefficient casualty departments.

Perhaps the most significant comment is expressed in the sixth conclusion of the report: "Equally, the service provided by general practitioners has a bearing on the way in which casualty departments are used by the public. Because of the importance of providing a service for relatively minor, non-urgent conditions, there is need for the fullest consultation between the hospitals and local medical committees (and other appropriate bodies) as to how general practitioners can help to relieve the hospital of the burden of such cases and so enable hospitals to concentrate on what they are best fitted to do. The question of employing general practitioners as clinical assistants should be explored, not only because there is undoubtedly a shortage of suitable junior staff, but because such a move would strengthen the essential links between the hospital and community services."

At first glance the problems outlined in "Casualty Services and their Setting" might appear to be peculiar to Great Britain and of little direct interest to Canadian readers. Further reflection, however, leaves one with the uncomfortable feeling that present difficulties in Britain may provide an all-too-accurate forecast of the future in Canada, particularly since governments have become increasingly involved in matters concerning all aspects of hospital services. This booklet therefore could be perused with profit by hospital administrators, directors of emergency departments, and particularly by those physicians charged with advising government commissions on hospital care.

Many of the problems discussed in this report may seem to some Canadian readers to be the result of the combination, peculiar to Britain, of venerable buildings and a socialized system of medicine. Consider, however, the daily scene in the emergency department of any Canadian hospital, even the newest and best equipped: an elderly lady with a Colles' fracture, fainting on a stool beside a grizzled workman soaking an ugly-looking infected finger; a man gravely ill with a coronary occlusion, separated by a flimsy curtain from the offensive bellicosity of a noisy drunk; or the patient who waits half a day to have his Potts' fracture treated because the staff surgeon concerned is occupied with other duties. Canada's hospitals are faced with potentially the same problems as those encountered in Great Britain, with every prospect that they will become more acute. The time seems particularly opportune for Canadian doctors to prepare to offer their carefully considered advice, particularly to provincial hospital commissions, on measures designed to forestall the problems that now plague the hospital casualty services in Britain. Now that government agencies control in large measure the financing of new hospital construction, they have assumed a

major obligation to ensure that public funds are wisely spent for this purpose. It is to be hoped that when the emergency departments of hospitals are being considered, full use will be made of this unusually provocative British report. W.R.H.

SALVAGE OF MEDICAL JOURNALS FOR DISTRIBUTION TO UNDERDEVELOPED COUNTRIES

THE avid hunger for all types of medical literature experienced by doctors in those areas of the world that are popularly referred to as "underdeveloped nations" has received brief comment in a previous issue (*Canad. M. A. J.*, 84: 618, 1961). Dr. Robert McClure of the Mission Hospital, Ratlam, India, during his recent visit to C.M.A. House, informed us that every medical journal received in that community is perused from cover to cover by the local Indian physicians as well as by the mission doctors.

We learn with considerable interest, therefore, that doctors in New Westminster, B.C., and its surrounding areas have established a committee of the Westminister Medical Association to conduct a program of salvage of used medical journals for despatch to hospitals, medical schools and individual physicians in underdeveloped and dollar-poor countries of Africa and the Far and Middle East. Contact with many medical school libraries in these countries has provided first-hand evidence that they have few or no medical journals and that they would welcome such periodicals, even those that are several years old, for "current" reading and reference.

Physicians and their office staffs in the New Westminster area are being asked to participate in this local salvage program by ensuring that all their used medical journals are saved for collection. The B.C. Society of Drug Travellers have volunteered to contribute to this project by collecting journals from physicians' offices, and the B.C. Pharmaceutical Association will arrange for the use of strategically located drug stores as collecting depots. Managers of these stores will package the journals in boxes which will be picked up by vans of the Western Wholesale Company, on whose premises space will be allocated for sorting and storage. Sorting and final packaging for shipment will be carried out by volunteer help. It is estimated that the cost of surface shipment of a complete 1961 volume of the *C.M.A. Journal* to India would be approximately forty cents if transported in ton shipments. The committee which organized this salvage program in New Westminster expresses the hope that UNESCO, WHO, and/or Colombo Plan funds will be forthcoming to assist in defraying shipping costs, and notes that shipments to Japan can be transported free, as freighter ballast. Import licensing procedures and distribution of this material at its destination would be cared for by authorities in the recipient country.

This program will first be put into effect in New Westminster and its surrounding areas, but Dr. Carl J. Reich, energetic chairman of the Westminster Medical Association's Committee for Salvaging Used Medical Journals, envisages a nationwide network of similar projects with a central co-ordinating committee to direct the ultimate disposal and distribution of salvaged periodicals to designated libraries and individuals throughout the needy countries of the world.

Dr. Reich invites all B.C. physicians to donate used medical journals to their pharmaceutical detail men for ultimate delivery, through the Westminster Medical Association, to medical libraries in Indonesia, the Philippines, Pakistan, India or Africa.

THE TEACHING OF "SCIENTIFIC ATHEISM" IN RUSSIAN MEDICAL SCHOOLS

FROM TIME to time, comments on various aspects of research, clinical investigation, medical education and practice and the nature of medical services provided to the public in the Soviet Union have appeared in the editorial and other pages of this Journal. These items have been published in the belief that a useful function may be served by supplying Canadian doctors with information concerning the activities and philosophies of our professional colleagues in Russia, fragmentary and indirect though such data may often be. The Journal is indebted in this respect to Dr. Wulf Grobin, whose outstanding linguistic abilities and background of training in European, British and North American centres of higher learning render him particularly well qualified to provide us with these fleeting glimpses of medicine in present-day Russia as reflected by the writings in current Soviet medical literature. In transcribing this material every effort is made to avoid any distortion of the intent of the original authors. That such information is presented solely as medical news, and that it in no way expresses the personal views either of Dr. Grobin or of this Journal's editorial staff, of course goes without saying.

Dr. Grobin has lately drawn to our attention a particularly intriguing article published in a recent issue of *Sovetskoe Zdravookhranenie*, a Soviet journal of public health, under the rather startling title, "Scientific Atheistic Propaganda in Medical Schools".

Two years ago, according to T. Ya. Tkachev, the author of this report (*Sovet. Zdravookhr.*, 1: 46, 1961), the Ministry of Higher Education of the U.S.S.R. recommended that a course on the basis of scientific atheism be instituted in Soviet medical schools. It was proposed that this course should consist of a total of 24 hours' instruction covering the following subjects: Marxist Atheism as the Highest Form of Atheism; The Origin of Religion; Present-Day Religions and Their Class Significance;

Canad. M. A. J.
May 27, 1961, vol. 84

Scientific and Religious Concepts; Critique of Religious Morality; The Attitude of the Communist Party and the Soviet Government to Religion and the Church; The Reason for the Existence of Religious Customs in the Soviet Union and the Means of Overcoming Them; and The Form and Methods of Scientific-Atheistic Education.

Lack of systematic cultural-educational instruction throughout the schools is identified as one of the reasons for survival of religious superstition in Russia, and the Soviet intelligentsia is exhorted to work toward the "atheistic education" of the labouring masses, as one of its "highest duties".

The author describes at length the methods employed in his medical school to indoctrinate students with the concepts of atheism. Every medical discipline from anatomy to psychiatry, he observes, presents opportunities for systematic demonstration, by incontrovertible evidence, of the inconsistency of religious doctrines. Particularly helpful, he finds, are the classical examples from medical history that illustrate religious excesses and misuse in the realm of medical theory and practice.

To those who expressed concern with the increasing problems confronting Canada's medical schools, in the Journal's recent Education Issue, it may provide some comfort, albeit cold comfort indeed, to learn that Soviet medical educationalists are encountering their own peculiar brand of obstacles and frustrations.

MEDICINE AND THE NEW AFRICA

IN CONSIDERING recent trends in the whole of Africa, with the development of independent African states, there is perhaps one point which has not been adequately stressed; this is that an alien and dominant culture has in the past been superimposed upon the original tribal habits. This dominant culture has made it obligatory for the native peoples to carry out instructions in more or less a passive sense, without their active participation. While colonial administrations are controlling particular territories, these instructions will be adequately carried out and respected. The big danger is, as is quite clear from what is happening in the Congo, that as soon as the colonial administration departs, the whole structure of government collapses. The main reason for this is not only the lack of trained and educated indigenous administrators, but a feeling on the part of the colonial peoples that they will now be completely free from the discipline imposed by European administration. It seems, therefore, that the inhabitants of these territories have been forced into a state of efficiency and competence which is in conflict with their basic inclinations. They have been forced to flower in the hothouse atmosphere of Western efficiency and productivity, and when the heat of Western interest is turned off, they may flower no more.

What we should therefore expect is that there may be a rather long latent period in many of these territories, accompanied by a certain measure of deterioration in administration, as well as in medical services, while the people themselves catch up with the vision of Western civilization which has been forced upon them. We should remember that it took the inhabitants of Great Britain more than 1000 years to regain the efficiency of administration practised by their erstwhile Roman masters.

The biggest mistake that we can make about the New Africa is to expect too much of these people, who are in most instances already doing their best to cope with their own problems as they see them, not as we see them. W.H.LEE.

STUDIES ON "GERIOPTIL" (COMPOUND H3)

"GERIOPTIL" is a preparation containing Professor Anna Aslan's much publicized compound H3 (diethylaminoethyl para-aminobenzoate procaine) together with a variety of vitamins and vitamin derivatives. Enthusiastic therapeutic claims had been made for this preparation, but there has been a lack of acceptable evidence of its value. The results of a controlled clinical trial in six subjects and six controls to study the effect of "gerioptil H3" on the mental ability, as measured by a number of psychological tests, in patients with senile or arteriosclerotic dementia have recently been reported by Cashman and Lawes (*Brit. M. J.*, 1: 554, 1961).

All of these patients were assessed psychologically before the trial was begun. The subjects were first given 0.5 ml. of 2% procaine subcutaneously, and then 2 ml. of 2% procaine intramuscularly, to obviate the possibility of procaine sensitivity. Following this they were given a course of 12 injections of gerioptil H3 intramuscularly over a period of one month. The control subjects were given similar injections of sterile water. Both subjects and controls received other treatment (sedatives, hypnotics and tranquillizers) during the trial, for their welfare and comfort, but no treatment was given which was listed by the manufacturer as contraindicated during gerioptil therapy.

This study produced no evidence that gerioptil was of any value in the treatment of these patients. The results suggested quite clearly that in those patients who did not receive the course of treatment the natural progression of their disease was retarded to some extent, while those who were treated with gerioptil deteriorated still further. In almost every part of each test, an effect contrary to the claims made for gerioptil seemed to have occurred. F.L.

LETTER TO THE EDITOR

THE PHYSICIAN AND THE PARA-MEDICAL PUBLICATION

To the Editor:

I have been a member of the editorial board of the medical newsmagazine, *M.D. of Canada*, since its inception in January 1960. I have resigned from this appointment recently and want my reasons for doing so to be a matter of record within the profession.

Early in September 1959 I received a letter which, after many flattering references to my standing in Canadian medicine, invited me to become a member of the editorial board of a new publication, *M.D. of Canada*. The writer, Felix Marti-Ibanez, was unknown to me but I had several friends in New York and assumed that Dr. Marti-Ibanez had my name from them. He also asked me to suggest another Halifax physician for the board. (I later learned that my nominee had been approached independently and that we had named each other, so that I do not know how M.D. Publications came to contact either of us originally.) On September 21, 1959, Dr. Marti-Ibanez in his capacity as president of M.D. Publications Inc. wrote to thank me for accepting the appointment, saying "We are most honored to have you as a member of the Board and we are looking forward to a long and fruitful association with you."

The first issue of *M.D. of Canada* appeared in January 1960. On March 3, 1960, I wrote Dr. Marti-Ibanez (who is Publisher and Editor-in-Chief of M.D. Publications), "I have examined the first two issues of *M.D. of Canada* with care. I have come to the conclusion that the primary function of this publication is to sell medical advertising. As yet it does not serve a serious scientific or professional purpose despite its distinguished patronage. You have invited me to take part in this commercial venture. Please define my contribution and remunerate me for the time needed for its performance. If it appears that I have no real function, then I should withdraw."

On March 14, 1960, Dr. Marti-Ibanez replied, "I am very disappointed to learn that, in your opinion, 'the primary function of this publication is to sell medical advertising.' I am equally sorry to hear that in your opinion 'it does not serve a serious scientific or professional purpose despite its distinguished patronage.' With all due respect, I would like to point out that your opinion represents such a minority that, as a matter of fact, it is the very first one in all the years of our existence, first in the United States and now in Canada, that we have had along those lines. The purpose of *MD* is *not* to sell medical advertising, but to offer our colleagues a panorama of all the cultural, professional and human aspects of the physician's life. Second, *MD* does serve a purpose, as confirmed by over 30,000 letters of praise received from physicians in the three first years of existence of the magazine in the United States. I sincerely hope that as time goes by you may change your opinion, as it will give me a great deal of personal pleasure to know that you agree with all our colleagues who like and admire *MD* and who appreciate the sincerity of our endeavor."

I would have withdrawn quietly from the editorial board then if I had not read the results of the hearings before the Kefauver Sub-Committee on Anti-trust and Monopoly as reported by Mr. John Lear, Science Editor of the *Saturday Review*.[1, 2] In brief, these articles reported that Henry Welch, the director of the Antibiotics Division of the U.S. Food and Drug Administration, had received in excess of one-quarter of a million dollars in seven years from the drug manufacturers. All these payments were channelled through MD Publications, a group that publishes the following medical and para-medical publications: *MD (A Medical Newsmagazine)*; *Antibiotics and Chemotherapy*; *Antibiotic Medicine and Clinical Therapy*; *International Record of Medicine* (Incorporating the *Quarterly Review of Ophthalmology*); *Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology*; *Quarterly Review of Surgery*; *Obstetrics and Gynecology*; *Quarterly Review of Pediatrics*. Both Dr. Henry Welch and Dr. Marti-Ibanez failed to appear before the Kefauver Sub-Committee, on grounds of ill-health, although Dr. Marti-Ibanez was able to go to Japan (to deliver a lecture on the history of medicine as a guest of honour at the annual meeting of the Japanese Society for Tuberculosis) a few weeks before.[1, 4]

This incredible story of the corruption of a highly placed government official by a physician who ostensibly was the owner and publisher of a group of reputable medical journals aroused no apparent concern among the medical profession in the U.S. or Canada (to my knowledge), although two members of the editorial board of *MD* resigned. *Newsweek*[4] said at that time (June 20, 1960): "Last week the scientists had startling statements to make about the publication to which they had lent their names: 'I used to be pleased to have my name on the board,' Dr. Norman Jolliffe, head of New York City's Bureau of Nutrition, told *Newsweek*. 'Now I'm disgusted. I've resigned from the board. I'm beginning to suspect all daily and weekly medical-news publications. I think they'd better discontinue.' Dr. Linus Pauling, Nobel Laureate Chemist, added: 'It may be that *MD Medical Newsmagazine* represents one of the many bad features about American medical practice.' "

The Kefauver hearings and the other published reports on the Welch scandal had left a great many questions unanswered. In September 1960, when in New York, I visited Dr. Marti-Ibanez, chiefly to discover whether he regarded a member of his editorial board as anything more than a figurehead. I concluded that he did not.

On May 1, 1961, I wrote Dr. Marti-Ibanez asking for candid answers to some of the questions relating to my continued service on the board.

"Since our discussion of September 28, 1960, I have carefully considered my position as a practising physician and a teacher of medicine in relation to further service on the editorial board of *MD of Canada*.

"So that I can be assured that my ethical position is not jeopardized by a continuing connection with your publication, candid answers to these questions are urgently required.

"What function is *MD of Canada* intended to perform?

"Why was I invited to join your editorial board?

Canad. M. A. J.
May 27, 1961, vol. 84

"I have been a member of your editorial board for more than a year and have not been asked to advise on, review, or edit any material. What function, then, do I, as a physician, serve on your editorial board?

"Who are the owners of MD Publications?

"You undoubtedly know that the printed record of the Kefauver Committee hearings is now becoming available and that copies of it are being circulated. The text includes a statement by Dr. Henry Welch to the effect that MD Publications is owned by yourself and two other parties. The record also carries the quotation from you indicating that you do not consider the identity of these other owners to be a public matter. I am not sure I understand why the information should not be public knowledge. In any case, I question whether the information should be denied to members of the editorial board of *MD*. I am sure you are aware of the several reports on the drug situation written by John Lear, Science Editor of the *Saturday Review* in New York. These reports have suggested that *MD's* ownership may be related to the McAdams Advertising Agency through Dr. Arthur Sackler. A copy of the printed record of the Kefauver Committee hearing which has come to me shows Dr. Sackler to be editor of one of the journals owned by MD Publications at the same time that Dr. Sackler was a key official in McAdams. This dual position can hardly be reassuring to the many physicians who fear growing drug-company domination of medical practice. Why were you, as one of the owners of MD Publications, willing to agree to give Dr. Sackler an editorial position while he held such a prominent place in the most powerful advertising agency in the drug field?

"Why did neither Henry Welch nor yourself appear before the Kefauver Committee and make a statement that would satisfactorily answer the allegations made against you?

"A candid response to these and similar questions is necessary when they are asked by the medical members of the editorial board. If you are unable to give me a satisfactory reply in the near future (May 15, 1961), I will feel free to take such action as is necessary to clear myself of any suggestion of unprofessional conduct that might arise from my association with your publication."

This letter was answered on May 8, 1961, by Miss Verna Sabelle, Executive Assistant to the Publisher, who said that Dr. Marti-Ibanez is, at the present time, in the Far East on a professional trip. Miss Sabelle was able to answer the serious questions I asked by sending me a reprint entitled "A Message to our Readers" signed by Dr. Marti-Ibanez.[5] I wish that space allowed extensive quotations from this apologia. It speaks for itself. Miss Sabelle also referred me to "A Message to Canadian Physicians", which was the publisher's message in the first issue of *MD of Canada* (January 1960, p. 1).

Neither of these essays sheds any new light on the matters discussed at the Kefauver Hearings. Miss Sabelle felt able to accept my resignation without consultation with Dr. Marti-Ibanez. I submitted it at once.

In summary, my objections based on esthetic criteria were enough to have prompted my resignation from this dummy board. My opinion is that these "medical newsmagazines" serve no serious professional purpose and are concentrated doses of pharmaceutical advertising disguised in a sugary capsule of pseudo-culture. Only the occasional critical reader is annoyed by the suffocating air of condescension and the pretence that this pasticcio of medical history, literary and social vignettes and sex is the actual cultural milieu of the physician. But, by and large, the physician can take this gaudy "throw-away" as a pleasant trifle or a waste of money, depending on his individual taste.

However, it is a more vital matter that this newcomer from the South, who appropriates the precious symbol of our profession, comes to us from a clouded parentage. It should disturb us that the identity and motives of its owners are unknown, even after Senate inquiry. What forces move behind this expensive, and superficially impressive, screen called *MD of Canada*?

What is the ethical position of the physician who has been asked to lend his name and presumably his reputation to this publication, sight unseen? Are only those physicians being "used" who are actually employed by such para-medical publications or who sit on the dummy editorial boards? If *MD* and *MD of Canada* are the kinds of journals I take them to be, this question must be faced by every member of the U.S. and Canadian editorial boards.

What is the ethical position of the physician who, either openly or covertly, works for the advancement of commerce, either for drug company, advertising agency or para-medical journal, in *conflict of interest* with his professional obligation? Any answer requires precise definition of the phrase "conflict of interest" but the testimony of Arthur S. Flemming, the (then) U.S. Secretary of Health, Education and Welfare, before the Kefauver Committee is pertinent. "Federal employment is a public trust. . . . It is not enough, in my opinion, for Federal employees to be innocent in fact of wrongdoing in outside activities in relation to their Government responsibilities. They must not even *have the appearance* [italics mine] of acting in private capacities contrary to the public interest they serve in their Government positions."

My purpose in this letter is to make it clear to my fellow physicians why I must dissociate myself unmistakably from the publications, *MD* and *MD of Canada*. I am making no new accusation or citing evidence that is not a matter of public record. I am urging no action except that we, as physicians, be scrupulous in guarding our professional integrity, especially from the taint of conflict of interest.

The implications for the profession and for the public good of the complex problems resulting from the impact of an intensely competitive industry (drug manufacturing) and the undisciplined, and often unscrupulous, activities of the advertising world (including its apparatus, the para-medical journal) on our profession are far-reaching and will remain with us for a long time. Further, I will not throw the baby out with the bath water in a blanket denunciation of the drug industry, as some critics have in the recent past. However, responsible executives in that industry have often been naïve and uncritical in yielding to the importunities of the sales staff over the objections of their medical departments. The most important guides the ethical drug manufacturers need in these troubled times are, that reasonable internal self-regulation helps maintain freedom and that their role as an important auxiliary in the provision of medical care demands a higher ethical standard than exists elsewhere in the market-place.

Perhaps, if we knew more about the activities of these groups we might be reassured but, in the mean-

time, individual physicians and organized medicine must examine their personal and corporate relationships to these our economic "allies" very closely. If the highest standards of professional conduct need to be urged, on other than ethical grounds, the physician can reflect that he will only deserve public support for his plea for continued professional freedom in the future if he proves, individually and as a member of organized medicine, that he is worthy of public trust now.

J. O. GODDEN, M.D.

77 University Avenue,
Halifax, N.S.

REFERENCES

1. LEAR, J.: *Saturday Review*, **43**: 37, June 4, 1960.
2. *Idem*: *Ibid.*, **43**: 37, July 2, 1960.
3. United States, Senate, Committee on the Judiciary, Subcommittee on Anti-Trust and Monopoly. Administered Prices: Hearings, May 17, 18, June 1, 2, 3 and 6, 1960. Pursuant to S. Res. 238, Part 22, Administered Prices in the Drug Industry. (86th Congress, 2nd Session.)
4. Medicine: *Newsweek*, **55**: 68, June 20, 1960.
5. MARTI-IBANEZ, F.: *Antibiotic Med.*, **7**: 411, 1960.

MEDICAL NEWS IN BRIEF

PHENYLKETONURIA

Research on the subject of phenylketonuria has included investigations of its incidence, methods of detection of carriers and of affected patients, of the metabolic defects involved, and of treatment and its results.

In Birmingham, England, a screening survey for phenylketonuria using Phenistix and covering about 98.8% of infants born in 1959 and living there at six weeks of age showed the incidence of this disorder to be about 1 in 20,000 births (*Brit. M. J.*, 1: 771, 1961). Three infants whose development proceeded normally were found to have intermittent weakly positive tests; their "carrier state" was not investigated.

Coates discusses the psychological aspects of 35 cases of phenylketonuria before and after dietary treatment (*Ibid.*, 1: 767, 1961), using the Griffiths mental development scale on children with a mental age below two years. Although many variables make it impossible to predict final intelligence levels, infant tests are still valuable as a method by which a child can be more validly compared with itself and changes in the degree of backwardness observed. From this series of 35 cases it was concluded that: (1) dietary treatment should be started as early as possible in all cases, and given up if no improvement of any kind occurs; (2) the fact that treatment is started early is no criterion by which to assess its final success; (3) if treatment is delayed, results are less likely to be good, but they may be good in about a quarter of the cases.

Moncrieff and Wilkinson (*Ibid.*, 1: 763, 1961) arrived at similar conclusions: (1) the detection and treatment of phenylketonuria in very young infants offers "a reasonable chance of preventing mental retardation"; (2) a routine test should be made at three weeks, except for babies with a family history of phenylketonuria; (3) treatment should be attempted in all cases; (4) treatment renders affected children more manageable even if their intelligence does not rise to satisfactory levels.

In Moncrieff and Wilkinson's series of 35 cases many difficulties were encountered: false positive and false negative urine tests occurred; individual variations in patients made the results of treatment unpredictable; in a few cases low-phenylalanine diets resulted in unsatisfactory growth of the infant. They recommend using available phenylalanine-free casein preparations and adding more milk than is usual in order to maintain satisfactory growth; dietetic control must be followed closely by serial estimations of blood phenylalanine levels. Whether or not dietary restrictions can ever be relaxed is not known; further investigation of the enzyme deficiency involved in this disorder is required. Further investigation of and development of more accurate and less costly means of detection of heterozygote carriers are also required.

NEW DRUGS FOR LEUKEMIA AND TUMOURS

The results of clinical trials of three new drugs, vincaleukoblastine, cyclophosphamide and uracil mustard, used in the treatment of the leukemias, of the allied reticuloses (lymphomas), and of malignant disease such as bronchial carcinoma, are reported in one of the "leading articles" in a recent issue of the *Lancet* (1: 265, 1961).

Vincaleukoblastine, an alkaloid from the periwinkle, *Vinca rosea* (Linn), has the formula $C_{46}H_{58}O_9N_4$ and contains indole and dehydroindole groups. Experimental reports were enthusiastic about its activity against leukemia and against tumour growth. Unfortunately, the clinical reports of several groups of investigators are much less enthusiastic. In addition, all investigators are greatly impressed by the severe toxic effects observed: severe temporary granulocytopenia, hemoglobin depression, profound hypoplasia of the bone-marrow, total alopecia, peripheral neurological disturbances, odd mental effects and severe mental depression. It is hoped that further studies will produce a new compound, more certain in action but less toxic, from this new group.

Cyclophosphamide and uracil mustard are two new members of the well-tried nitrogen-mustard group. They represent recent attempts to develop nitrogen-mustard compounds that will be activated only at their site of action, and that can be given orally or suspended in stable solution for intravenous or intramuscular use.

Cyclophosphamide was found to be effective against some animal tumours. Clinical reports indicate that it may be useful, particularly against the chronic leukemias and reticuloses. Side effects are not often troublesome, but severe hematological depression may occur; a close watch must be kept on the white cell count.

In uracil mustard the nitrogen-mustard group is attached to a pyrimidine base, in the expectation that it will be absorbed into areas of maximum nucleic acid activity. Uracil mustard was found effective against experimental leukemia in animals. Results of clinical trials indicate that it is the most effective oral drug of this group so far used. Side effects are rarely serious. However, all the precautions needed with the older nitrogen-mustard drugs, especially regular blood counts, must be taken with both uracil mustard and cyclophosphamide.

(Continued on advertising page 28)

Canad. M. A. J.
May 27, 1961, vol. 84

ASSOCIATION NOTES

EXECUTIVE COMMITTEE MEETING
MAY 3 and 4, 1961

The Executive Committee met at C.M.A. House on Wednesday, May 3, and Thursday, May 4, 1961. Dr. F. S. Hobbs, President of the B.C. Division, represented that Division in lieu of Dr. Peter Lehmann, who was unable to attend owing to illness. Dr. M. R. MacCharles of Winnipeg was present as an observer, at the request of the Manitoba Division.

The minutes of the meeting of February 24, 1961, were adopted with minor alterations in wording.

Establishment of Association Gold Medal Award

The Executive Committee, as recorded in reports of previous meetings, had referred to the Committee on Awards, Scholarships and Lectures, a proposal for the establishment of an award to be known as The Canadian Medical Association Gold Medal. After due consideration of this proposal the Committee on Awards, Scholarships and Lectures reported that it does not recommend the creation of such an additional award. The Executive Committee unanimously affirmed its approval of the principle of an award of this nature as proposed by the *ad hoc* committee composed of Dr. E. K. Lyon, Dr. R. Lemieux and Dr. W. Wigle, and recommended that this matter be the subject of further discussion between Dr. Lyon and the Chairman of the Committee on Awards, Scholarships and Lectures. The result of this discussion is to be reported to the Executive Committee at its next meeting just prior to the annual meeting of the General Council.

Costume Jewelry Pins for Presentation to Past Presidents' Wives

The action of the General Secretary in arranging for the design and purchase of suitable pins in the form of costume jewelry, for presentation to the wife of each Past President of the Association, was approved.

Membership Fees

The Executive Committee directed the Honorary Treasurer to investigate the question of the optimum level of financial reserves that should be maintained by the Association, and present a statement thereon at the Committee's next meeting. With such information the Committee would be better prepared to discuss the adequacy of the existing membership fee and the necessity of any increase in this fee at the present time. Recommendations arising from such discussion will then be forwarded to General Council.

Approval of Training and Standards for Inhalation Therapists

The General Secretary reported that according to information supplied to him, there are approximately 75 inhalation therapists in Canada at present. Their duties vary widely from hospital to hospital. In some centres they are well-trained technicians whose activities include the administration of oxygen, oxygen and carbon dioxide mixtures, helium and various aerosols; the humidification of the gases involved; and the operation, care and maintenance of the equipment required for this purpose. In recent years such personnel have also been increasingly engaged in the care and operation of positive-pressure breathing apparatus. In some hospitals, however, these technicians are permitted no direct responsibility for the foregoing duties. Their present training curriculum varies greatly. In some cases this is provided by a one-year period of apprenticeship, in other instances by a lecture course only.

The Canadian Anaesthetists' Society, through its Quebec Division, has requested that the C.M.A. consider the establishment of an official body with responsibility for approval of training and standards for inhalation therapists, emphasizing the opinion that there is now a distinct need for official medical guidance of such personnel.

The Executive Committee directed its Chairman, in consultation with Dr. G. Halpenny, to appoint three representatives from the C.M.A. to attend a meeting to be held in June under joint sponsorship with the Canadian Anaesthetists' Society and the Canadian Thoracic Society, to discuss this proposal and to make recommendations thereon.

The Executive Subcommittee on Health Services

Dr. G. E. Wodehouse, Chairman of the Executive Subcommittee on Health Services, reported that a draft document had been prepared as a suggested outline for the preamble of documentary presentations or briefs that the Divisions and medical affiliates of the Association might submit before the Royal Commission on Health Services. Copies of this draft preamble outlining the general characteristics of the Canadian medical profession were circulated to the Divisions. Some of the comments submitted in reply were uncritically laudatory; one from the Nova Scotia Division made specific proposals for improvement. The Executive Subcommittee itself, after further study, feels that several additional changes in this document are required but before it is rewritten the comments of the Association's affiliated medical societies will be awaited.

The Chairman of the Subcommittee noted that its work has been handicapped by the lack of terms of reference of the Royal Commission on Health Services but that this should not slacken the activities of the Subcommittee, the Divisions or the Affiliated Societies in preparing material for presentation to the Royal Commission.

It was agreed that when the Royal Commission's terms of reference are made available they should be (a) announced in the "News and Views on Medical Economics" section of the C.M.A. Journal, (b) circulated immediately to all Divisions and Affiliated Societies, and (c) discussed in a specially convened meeting of the Executive Subcommittee. In addition, immediately on receipt of the Royal Commission's terms of reference, arrangements will be made for a meeting of key personnel from the Divisions who will be responsible for the drafting of Divisional submis-

sions. At a later date the Affiliated Societies will be invited to a briefing session.

After examination of the script of a radio broadcast on *The Nation's Business* delivered on April 14 by the Minister of National Health and Welfare, the Executive Subcommittee considered that this address reflected the attitude of the Government party toward major issues in health services and authorized the General Secretary to request the Minister's permission to edit and publish significant passages from his broadcast. With Mr. Monteith's permission, this material was published in the C.M.A. Journal of May 6.

This prompted discussion of the advisability of inviting representatives of other political parties to acquaint the Executive Subcommittee members with their views and to facilitate the familiarization of such party representatives with the principles and policies of the C.M.A. The advisability of holding such discussions was debated at considerable length by the Executive Committee. It was considered highly undesirable that any action be taken that might be interpreted as indicating alignment of the C.M.A. with any political party, or its opposition to the policies of any other party. The Executive Committee expressed the general view that official contacts of the Association should be confined to those with the Government of Canada rather than with any political party, as such, and that after the Royal Commission on Health Services has been constituted, all official negotiations within its purview should be conducted with that body only.

It was agreed that the following procedure should be adopted in the presentation of submissions by the C.M.A. to the Royal Commission: The President of The Association shall introduce the members of the C.M.A. delegation; the General Secretary shall present the submission; and the other members of the Executive Subcommittee on Health Services shall be present as official spokesmen of the C.M.A. to enter into such discussion as may be appropriate.

The Chairman of the Executive Subcommittee on Health Services also presented a brief progress report on the collection of data for incorporation in a presentation on the state of medical manpower in Canada. Basic information on registration and the effect of immigration is being sought from the provincial licensing authorities, and the compilation of national statistics is awaiting the last of their replies. The Royal College of Physicians and Surgeons of Canada has provided a useful breakdown of specialists but it was also decided to request comment from the Affiliated Societies concerning the supply and distribution of specialists in their fields, with comment relative to any outstanding shortage and the optimum ratio of population per specialist in the category of each specialty. It is anticipated that it might be desirable, possible and necessary to collect similar data with reference to hospitals according to their type, size and distribution, and that such information might also be sought with regard to diagnostic facilities. The Executive Subcommittee's discussions on manpower extended to the supply of adequate numbers of properly qualified medical undergraduates, the possible need of additional medical schools and the possibility that financial assistance from public funds might be required to aid undergraduates. It was agreed that these considerations were within the interests of the Association of Canadian Medical Colleges, which should be encouraged to express opinions and recommendations on these topics.

Appropriate members of the C.M.A. staff were encouraged to elaborate draft documents on needs, resources and quality of medical services as the pressure of their current duties permits.

The General Secretary commented on recent conversations with Chief Justice Hall, Chairman of the Royal Commission on Health Services, and with officials of the Department of National Health and Welfare. According to information from these sources, the terms of reference of the Royal Commission are under active discussion but at this writing no final decisions have been taken in this regard at cabinet level. The Commission Chairman expressed the opinion that these terms of reference would be promulgated in the very near future. The General Secretary in conversation with these officials again emphasized that the C.M.A. strongly recommends that the Royal Commission's terms of reference should extend to the broadest latitude and that these terms should in no way restrict the purview of its studies.

The Executive Subcommittee on Health Services is scheduled to meet again on May 12 and 13.

Press Conference on Radiation Hazards

The General Secretary reported a communication from the President of the Canadian Association of Radiologists expressing concern over the promulgation of misleading information to the public about the damaging effects of exposure to small amounts of ionizing radiation, especially misinformation regarding the harmful effects from common diagnostic procedures carried out by competent, qualified radiologists. The Canadian Association of Radiologists therefore propose that representatives from that organization and from the C.M.A. should discuss this topic in a press conference at the time of the 94th Annual Meeting in Montreal in June. This proposal was approved by the Executive Committee, the C.M.A. representatives at this press conference to be selected by the Chairman of General Council and the General Secretary.

Canadian Centenary Council

The Canadian Centenary Council comprises a number of national organizations that have banded together to plan a program of activities for Canada's centenary in 1967. The General Secretary recommended that the C.M.A. accept an invitation to join this Council, since the Association may well obtain useful information and assistance in planning our own centenary program in the same year. The Executive Committee were in agreement with this proposal and designated the Secretariat to represent the C.M.A. on the Canadian Centenary Council.

British Commonwealth Medical Conference

Dr. T. J. Quintin, the Association's delegate to the British Commonwealth Medical Conference in Auckland, New Zealand, February 1 to 4, 1961, in his report to the Executive Committee, noted that a major feature of the Conference agenda was the discussion concerning the proposed creation of a Commonwealth Medical Association. Dr. Quintin represented the C.M.A. as being opposed to the formation of a new medical association with expensive centralized admin-

Canad. M. A. J.
May 27, 1961, vol. 84

istrative and secretarial facilities and an additional journal. He expressed the view that this Association considers that its international activities should be concentrated in programs dedicated to the advancement of world medicine, through the World Medical Association, and that the British Commonwealth Medical Conferences as they have been conducted to date provide adequate opportunity for discussions of individual and mutual problems between representatives of the various national medical associations within the Commonwealth.

After considerable deliberation the Executive Committee directed the General Secretary to reply to the invitation to sponsor the formation of a Commonwealth Medical Association in the following terms: Although critical of many aspects of the proposal to form a Commonwealth Medical Association, the C.M.A., recognizing its obligations as a senior member of the Commonwealth, is reluctant to withdraw. However, this Association expresses its unwillingness to become a sponsoring member of the proposed Commonwealth Medical Association and recommends that the British Commonwealth Medical Conferences should be continued as in the past until such time as more definite aims and objects are evolved and practical means for their implementation have been devised.

Invitation to Submit a Brief Before the Restrictive Trade Practices Commission Concerning Alleged Illegal Price Fixing of Certain Drugs

The General Secretary reported that during the past year an investigation of alleged illegal fixing of prices for antibiotics and ataractic drugs has been in progress under the auspices of the appropriate federal agency.

The C.M.A. has recently been invited to present submissions at forthcoming hearings of the Restrictive Trade Practices Commission, on the subject of costs, mark-ups and retail prices of these drugs with particular reference to any evidenec that would indicate the existence of illegal price-fixing procedures. In consultation with the Chairman of the Association's Committee on Pharmacy, it was considered that if the purview of such hearings is to be confined solely to the economic aspects of drug pricing, the C.M.A. would become involved in an area in which it is currently uninformed and unqualified to express responsible opinions without further prolonged and intensive study. The Executive Committee agreed that since the nature of this investigation is to be confined, to all intents and purposes, to the economics of drug pricing, the C.M.A. would not be suitably qualified to present submissions at hearings of the Restrictive Trade Practices Commission. The Committee also recommended that its reasoning in arriving at this decision should be explained in detail to General Council at its forthcoming meeting.

Proposed C.A.M.S.I. Fund For Assistance to Undergraduate and Postgraduate Medical Trainees

As recorded in reports of previous Executive Committee meetings, the Canadian Association of Medical Students and Internes has been holding discussions with representatives of the Association of Canadian Medical Colleges and the C.M.A. concerning C.A.M.S.I. proposals for the establishment of a fund to provide loans and bursaries to aid in undergraduate and postgraduate medical training. The C.M.A. delegates participating in these discussions are Dr. W. G. Cosbie and Dr. C. C. Ross. The General Secretary presented a summary of Dr. Cosbie's report of these discussions to date which, in brief, expressed the opinion that the procedure proposed by C.A.M.S.I. for the creation and maintenance of such a fund does not appear to be sound or practical.

Reports of Standing Committees

The reports to General Council from the Association's various Standing Committees and the reports of the Honorary Treasurer, the Managing Editor and the Editor of C.M.A. Publications were received, discussed and accepted for presentation to General Council at its meeting in June. Certain of these reports were supplemented by additional comment from the Executive Committee. The reports of all standing committees will be published *in extenso* in the Transactions of the 94th Annual Meeting.

The Executive Committee also

—Delegated as C.M.A. representatives, Dr. John Stapleton, Chairman of the C.M.A. Committee on Approval of Schools for Radiological Technicians, and Dr. A. F. W. Peart, Deputy General Secretary, to attend a Conference on Technical Training being held in Ottawa on May 9 and 10, under the auspices of the Department of Labour.

—Appointed Dr. Harry Morton of Montreal as C.M.A. representative to the Emergency Health Services Advisory Committee now being constituted on recommendation of the Minister of National Health and Welfare, with Cabinet approval. This Committee will assume the duties formerly assigned to the Defence Medical and Dental Services Advisory Board (D.M.D.S.A.B.), which has disbanded. In the event that Dr. Morton is unable to accept this appointment the General Secretary was authorized to arrange for an alternate delegate of his choice to represent the C.M.A. on E.H.S.A.C.

—Named Dr. Gustave Auger of Quebec, Que., as this Association's representative on the National Medical Advisory Committee of the Canadian Council for Crippled Children and Adults.

—Nominated Dr. Nathan Levinne and Dr. A. F. W. Peart as C.M.A. delegates to attend the 1961 Assembly of the Canadian Hospital Association, to be held in Toronto on May 24 to 26.

—Appointed Dr. A. D. Kelly as C.M.A. representative at the Canadian Welfare Council's Conference on Recreation and Leisure, to be held in Ottawa on May 15.

—Delegated Dr. A. D. Kelly to represent the Association at a conference in Ottawa which is being arranged by several of the provincial Alcoholism Foundations, for the purpose of creating a National Federation of Alcoholism Foundations.

—Appointed Dr. R. O. Jones, Dr. W. Wigle and Dr. Paul Melanson to serve as the Committee on Committees for the 1961 meeting of General Council.

—Supported a recommendation by the Committee on Public Relations that arrangements be made to include bilingual wording on the official C.M.A. crest.

The next meeting of the Executive Committee will be held on June 16 and 17 immediately preceding the annual meeting of General Council.

94TH ANNUAL MEETING: THE LADIES' PROGRAM

THE MOST BEAUTIFUL MONTH IN MONTREAL IS JUNE

The two main events of the Ladies' Program at the Canadian Medical Association meeting in June will be a lunch on Wednesday, June 21, at the Montreal Museum of Fine Arts, 1379 Sherbrooke Street West, and a lunch at the Queen Elizabeth Hotel in the Marquette and Jolliet Rooms on Thursday, June 22.

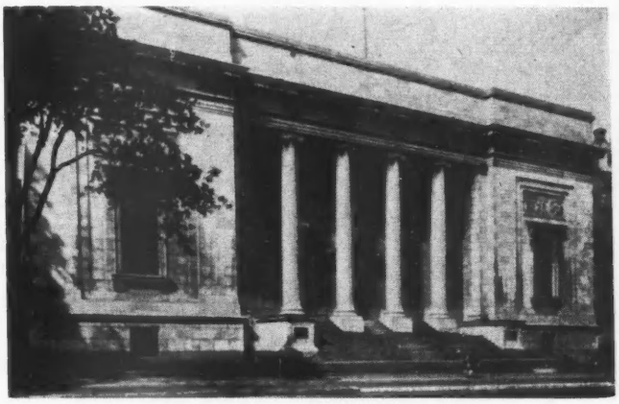
Lunch at the Museum will be served upstairs in the beautiful main gallery, where the special exhibit "Doctors and Art" will be on display. This exhibit consists of paintings and sculpture owned by doctors in the Montreal area. A selection has been made to cover old masters, impressionists, and paintings by popular Canadian artists from early periods right to the most "avant-garde". After the buffet lunch a short guided tour of the Museum has been arranged to show the highlights of the collection, and as there will be many guests from other provinces, it was felt that the rooms furnished with early Quebec furniture might be of special interest.

Briggs

Mrs. William Mackersie, President of the Woman's Auxiliary to the American Medical Association, and speaker at the luncheon on June 22.

A draw for two artistic door prizes will be made during lunch. The committee is very excited about these prizes and hopes that our guests will be equally pleased. One is a framed Eskimo sealskin block print entitled "Birds from the Sea", created by a woman artist who lives at Cape Dorset. The other door prize is a beautiful ceramic plate, suitable for hanging as a wall decoration, specially designed for this event by Jordi Bonet, a Spanish painter living in Montreal, who as well as being a painter is a skilled craftsman in ceramics.

At the lunch on Thursday at the Queen Elizabeth Hotel, Mrs. William Mackersie, President of the Woman's Auxiliary to the American Medical Association, will be the guest speaker and will discuss the importance of the Auxiliary in supporting the work of the Medical Association, and the necessity for women to help create unity and co-operation among medical groups. There are many facts concerning the medical profession about which the public needs to be informed, and here women can be of great service in the promotion of good public relations. Mrs. Mackersie has had wide experience and is known as a gifted speaker. A Canadian by birth, from Belwood, Ontario, she became President of the Woman's Auxiliary at the 37th Annual Meeting in 1960. We are very honoured to have Mrs. Mackersie as our guest speaker.



The Montreal Museum of Fine Arts.

Another outstanding event at the lunch will be a fur show of latest fashions in Canadian furs presented by the Fur Trade Association of Canada Inc. An interesting feature of the luncheon, especially for six lucky winners, will be door prizes of six beaver hats, fashioned in the latest styles. The skins for these hats have been donated by the Department of Fish and Game of the Province of Quebec. Six professional models will display the hats and as the number of the lucky winner is drawn, she may take her choice—first number drawn, first choice of hat. Alterations will be made to fit the head size of the winners before they leave Montreal. The Fur Trade Association of Canada Inc. are also providing favours of a rose and perfume for every guest.

Mrs. S. A. MacDonald and Madame Paul Robert, Co-Chairmen in charge of Entertainment, tell us that there is ample room at both luncheons for everybody and they hope to see all doctors' wives attending the meeting at these two events, which have been planned in the best traditions of Montreal hospitality.

In a subsequent issue of *The Canadian Medical Association Journal* announcement will be made of final details of the ladies' program, including the golf tournament.

MARY WEIL

GOLFING FACILITIES AND TOURNAMENT

Golfing appetites of all visitors to the Annual Meeting can be satisfied by the fine facilities available in the Montreal area. Many of the championship courses have been made available to doctors and their wives during this time. Arrangements can be made at the time of registration for a round of golf on any day.

Everyone interested is asked to register for the Golf Tournament which will be held at the Royal Montreal on Thursday afternoon, June 22. A good tournament is anticipated. The annual competition for the Ontario and Alberta Cups will be held. In addition this year, the Quebec Cup will be placed in competition for the first time. It will be given for individual low net honours.

The Eaton Trophy, emblematic of the women's championship, will be competed for on Thursday morning, June 22, at the Mount Bruno Golf Club.

Canad. M. A. J.
May 27, 1961, vol. 84

INFORMATION FOR CANADIAN DOCTORS ON

FINANCIAL ASSISTANCE AVAILABLE FOR GRADUATE OR POSTGRADUATE MEDICAL STUDY

in

CANADA - UNITED STATES - EUROPE

(PART 4*)

Through its Journal, The Canadian Medical Association is pleased to provide up-to-date information on financial assistance that is available to facilitate the graduate and/or postgraduate medical education of Canadian doctors. Owing to space limitations, we are not in a position to publish the complete list of medical award classifications at this time. Please refer to other issues of the Journal, if the subject in which you are interested is not listed herein.

Unless otherwise indicated, the value of the awards will be quoted in the currency of the country mentioned. As entry regulations into a foreign country vary, it is recommended that the applicant for postgraduate study first investigate all details through the Embassies of the foreign countries concerned. Applicants should satisfy themselves whether medical registration in the jurisdiction of the award is or is not a requirement to hold the postgraduate post in the country selected.

In so far as entry into the United States is concerned, simply communicate with the U.S. consular office nearest your place of residence. These offices are located in the following cities: St. John's, Newfoundland; Halifax, Nova Scotia; Saint John, New Brunswick; Quebec, Quebec; Montreal, Quebec; Ottawa, Ontario; Toronto, Ontario; Windsor, Ontario; Winnipeg, Manitoba; Calgary, Alberta; Edmonton, Alberta; and Vancouver, British Columbia.

It is understood that a Canadian citizen entering the United Kingdom must have a valid passport but that no visa is necessary. Application forms for passports can be obtained at any large Canadian Post Office and should be completed and sent to the Chief Passport Officer, Ottawa, Ontario.

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
MEDICINE — CANADA							
University of Toronto: Dr. Arthur F. Haasz Fellowship	Teaching and research in medicine	University of Toronto; in special circumstances in other centres	$2500	One	Unspecified	Awarded to a graduate of an approved medical school for teaching and/or research	Professor of Medicine, University of Toronto, Toronto 5, Ont.
John McCrae Fellowship		McGill University	$1000 per annum	One	One year	Must be a candidate for a diploma in surgery, urology, otolaryngology or radiology at McGill University or be proceeding to a McGill M.Sc. or Ph.D. in fields related to the above subjects; open to men students only	Dean, Faculty of Medicine, McGill University, Montreal, P.Q., by May 1
Dr. David A. Stewart Memorial Scholarship	Undergraduate medical studies	University of Manitoba	Dependent on the need of applicant	Unspecified	One to four years	Applicant must be a resident of Manitoba, and upon graduation, must practise his profession in rural Manitoba or on the staff of the Manitoba Department of Health and Public Welfare for a number of years equal to that in which he was in receipt of assistance	Department of Health and Public Welfare, Winnipeg 1, Man.
University of Western Ontario: John McLary Memorial Fellowship	Research in industrial medicine	University of Western Ontario	Income from endowed fund	One	One academic year	Open to graduates in medicine from any approved Canadian university	Dean, Faculty of Medicine, University of Western Ontario, London, Ont.
University of Western Ontario Research Fellowships in Medicine	Medicine, any basic science or clinical department. These are: anatomy, anesthesia, bacteriology and immunology, biochemistry, biophysics, medical research, medicine, microscopic anatomy, pathology and preventive medicine, obstetrics and gynecology, radiology and surgery	University of Western Ontario	Variable	Variable	Unspecified	Open to graduates in medicine from any approved Canadian university	Dean, Faculty of Medicine, University of Western Ontario, London, Ont.

*See also page 1038, May 6; page 1092, May 13; page 1148, May 20.

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
Ciba Medical Research Fellowship	Training in and promotion of medical research in Canada	Canada	$5000, plus grant of $500 to department and $500 for travel and books, etc.	One	One year (July 1-June 30); in special circumstances may be renewed for second year	Applicant must be a graduate of approved medical school and be prepared to spend a year in medical research, basic or clinical, in Canada. Open on equal terms to men and women	C. Walter Murphy, M.D., Fellowship Officer, CIBA Company Limited, 200 Metropolitan Blvd., Dorval, Que.
MEDICINE — UNITED KINGDOM							
Wandsworth Scholarship	Medical research	London School of Hygiene and Tropical Medicine, and overseas if necessary	£300 per annum (or more in suitable cases), plus transportation and allowance for overseas	Approx. one every two years	Two or three years (renewable)	Available to nationals of all countries but preference given to British nationals; must have post-graduate medical or scientific qualifications	London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C. 1, England
Graduate Research Scholarships	Approved research projects in any branch of the medical sciences	In a department within the Faculty of Medicine of the University of Edinburgh	£500 per annum for 1st year £600 per annum for 2nd year	Four offered annually	Two years Tenable from October of each year	Open to graduates in the Faculty of Medicine; to graduates in the Faculties of Arts and Science of any university who hold an Honours degree: and to Licentiates in Medicine Scholarships shall not be open for award to any applicant who, excluding any period spent in National Service, has held a degree or licence for longer than three years Approved whole-time work	Applications for Scholarships and Fellowships on prescribed forms to be lodged with the Dean of the Faculty of Medicine, University of Edinburgh, Teviot Place, Edinburgh, Scotland
Graduate Research Fellowships	Approved research projects in any branch of the medical sciences	In a department within the Faculty of Medicine of the University of Edinburgh	£700 per annum for 1st year £800 per annum for 2nd year and where awarded for 3rd year, £900 per annum	Three offered annually	Two years Tenable from from October of each year	Open to graduates in the Faculty of Medicine; to graduates in the Faculties of Arts and Science of any university who hold an Honours degree: and to Licentiates in Medicine Scholarships shall not be open for award to any applicant who, excluding any period spent in National Service, has held a degree or licence for longer than three years Approved whole-time work	Applications for Scholarships and Fellowships on prescribed forms to be lodged with the Dean of the Faculty of Medicine, University of Edinburgh, Teviot Place, Edinburgh, Scotland
University of Edinburgh Wilkie Research Fellowship	Research in surgery and/or medicine	University of Edinburgh	£800 to £900 per annum with possibility of allowance for approved expenses of research	One	Two years (renewable)	None	The Dean, Faculty of Medicine, University of Edinburgh, Teviot Place, Edinburgh, Scotland
Foulerton Gift Research Fellowship	Medicine	Any approved place	£950 to £1350 per annum	One	Two to five years	Open to persons under 35 who are, and whose father and grandfather are or were, British nationals. Graduates of non-U.K. universities eligible to apply. Offered about every 2-5 years	Assistant Secretary, The Royal Society, Burlington House, London, W. 1, England
Medical Clinical Scholarship	Medicine	Oxford University Medical School	£470 per annum	One in alternate years, in rotation with New Zealand, South Africa, Australia	Three to five years	Award to medical student to enable pursuit of clinical studies	Secretary of the Medical School, Osler House, 43 Woodstock Road, Oxford, England
MEDICINE — UNITED STATES							
University of Nebraska Scholarships and Fellowships	Postgraduate study and research	University of Nebraska College of Medicine	$500 to $1200	Limited	Unspecified	Open to qualified students admitted to and enrolled in the University College of Medicine; Canadians eligible	The Dean, University of Nebraska College of Medicine, Omaha 5, Neb.
University of Missouri Curators Grant-in-Aid for Foreign Students		University of Missouri, Columbia, Mo.	Tuition and other fees	25 (competing with candidates in other disciplines)	One academic year (renewable)	Available to graduate students outside U.S.A.	The Dean of Graduate School, University of Missouri, Columbia, Mo.

Name of Award	Field of Study	Where Tenable	Value	Number Available	Duration	Conditions	Apply to
MEDICINE — UNRESTRICTED							
The Canadian Medical Association—Osler Scholarships (2)	"To pursue special studies to advance the knowledge of medicine and to improve the teaching of clinical medicine"	Unrestricted	Approx. $800	Two awards every three years	One year	The capital sum is held in the custody of The Canadian Medical Association and the revenue is used to provide two scholarships every three years. One candidate is nominated by the Faculty of Medicine, McGill University, and the other by the Medical Board of the Montreal General Hospital. Available to graduates in medicine who are known and recommended by these nominating bodies	The Canadian Medical Association, 150 St. George St., Toronto 5, Ont.
Sir Edward W. Beatty Memorial Scholarships		McGill University, or elsewhere in Canada or abroad	$1500	Two	One year	Available to nationals of all countries; must be registered in Faculty of Medicine of McGill University as candidates for M.D. or C.M. degree, or one of the postgraduate diplomas in a clinical specialty. Recipients undertake research or special training excluding normal training for above degrees or diplomas. For students working toward the M.D. or C.M., award may be held at any approved institution in Canada or abroad; for other qualified students, award must be held at McGill University	Secretary, Faculty of Medicine, McGill University, Montreal, by February 1
Dr. Edith Pechey Phipson Postgraduate Scholarship for Women		Unrestricted	£105 per annum	One	One year (renewable)	Available to women from all countries; must hold recognized medical qualifications. Award is to enable recipients to undertake postgraduate medical studies	University of London Royal Free Hospital School of Medicine, 8 Hunter Street, London, W.C. 1, by May 1
METABOLISM AND ENDOCRINOLOGY — CANADA							
University of Saskatchewan: Fellowship in Metabolism	Metabolism and endocrinology (research)	University Hospital, University of Saskatchewan	$4000	One	One year	Candidate must have had at least two years' postgraduate training in medicine and be proceeding to specialization in internal medicine	Dr. I. M. Hilliard, Professor of Medicine, University of Saskatchewan, Saskatoon, Sask.
MICROBIOLOGY — UNITED STATES							
Rutgers University: Waksman-Merck Postdoctoral Fellowship in Microbiology	Training in: biochemistry, microbial chemistry, microbiology, immunology and related sciences	Rutgers, The State University	$5500	One per year	One year	Open to persons who have received or are about to receive the Ph.D. degree or equivalent degree	Director, Institute of Microbiology, Rutgers, The State University, New Brunswick, N.J.
MICROBIOLOGY AND PATHOLOGY — UNITED KINGDOM							
London University (Lister Institute of Preventive Medicine): Jenner Memorial		Lister Institute	£350 to £500* *Subject to revision	One	One to three years	Open to British subjects. Vacancies advertised in medical journals	Secretary, Lister Institute of Preventive Medicine, Chelsea Bridge Rd., London, S.W. 1, England
MICROBIOLOGY, PHYSIOLOGY OR NUTRITION — UNITED KINGDOM							
Queen Elizabeth College Postgraduate Scholarships	Research in microbiology, physiology or nutrition	Queen Elizabeth College, University of London	£350 to £400	Two	One year (possible renewable two)		Secretary, Queen Elizabeth College, London University, London, England
MIDWIFERY — UNITED KINGDOM							
Annie McCall Postgraduate Fellowship in Midwifery	Research in midwifery	United Kingdom	£1500 per annum	One (available when vacant)	Maximum three years	Available to women of all countries; must have a higher medical or surgical qualification and ability for original research work	Royal Free Hospital School of Medicine, 8 Hunter Street, London, W.C. 1, England, by May 1

(To be continued)

MEDICAL MEETINGS

L'ASSOCIATION DES MEDECINS DE LANGUE FRANCAISE DU CANADA

31e Congrès, Château Frontenac, Québec, P.Q.,

Le 5-7 juin, 1961

PROGRAMME SCIENTIFIQUE

Lundi, le 5 juin

8 h. à 10 h.:	(a) Cours de Chirurgie: "Les vaisseaux périphériques". (b) Cours de Médecine: "Les entéro-virus".
10 h. 15 à 12 h. 15:	Télévision en couleurs: "La Gastrectomie".
1 h. 30 à 3 h.:	Symposium: "Les familles canadiennes françaises et leurs maladies".
3 h. 30 à 5 h.:	Travaux originaux.
5 h.:	Conférencier invité, le Dr Rocke Robertson, professeur à McGill: "Thrombose veineuse: étude clinique et expérimentale".

Mardi, le 6 juin

8 h. à 10 h.:	(a) Cours de Chirurgie: "Foie, voies biliaires et pancréas". (b) Cours de Médecine: "Les actualités en endocrinologie".
10 h. 15 à 12 h. 15:	Télévision en couleurs: "La mastectomie".
1 h. 30 à 3 h.:	Forum: "L'athérosclérose".
3 h. 30 à 5 h.:	Travaux originaux.
5 h.:	Délégué officiel de France.

Mercredi, le 7 juin

8 h. à 10 h.:	(a) Cours de Chirurgie: "Soins pré et post-opératoires". (b) Cours de Médecine: "Les progrès récents dans les anti-coagulants".
10 h. 15 à 12 h. 15:	Télévision en couleurs: "Le goître".
1 h. 30 à 3 h.:	Colloque: "Les actualités en obstétrique".
3 h. 30 à 5 h.:	Assemblée générale d'affaires.

Séances de télévision

Responsable: Dr Wilfrid Caron.
Assistant: Dr Jean Couture.

Lundi, le 5 juin

Gastrectomie

Animateur: Dr Jacques Turcot.
Chirurgien: Dr François Roy.
Jury: Dr Jean-Paul Dugal, Dr Roland Cauchon et Dr Rocke Robertson.

Mardi, le 6 juin

Mastectomie

Animateur: Dr Wilfrid Caron.
Chirurgien: Dr Hector Beaudet.
Jury: Dr Maurice Thibault, Dr Louis-Alexandre Frenette et Dr Jacques Brunet.

Mercredi, le 7 juin

Goître

Animateur: Dr Jean-Marie Lemieux.
Chirurgien: Dr Florian Trempe.
Jury: Dr Eucharistе Samson, Dr Charles Plamondon et Dr Yves Morin.

Travaux originaux

Lundi, 5 juin

1. Drs Jacques Ducharme et P. P. Collip: Atrésie de l'œsophage, importance du diagnostic précoce, de l'approche extrapleurale et du nursing intensif.
2. Drs A.-F. Vallée et J.-G. Ouimet: La bronchographie trans-crico-thyroïdienne percutanée: technique et résultats.
3. Dr Leo J. Mahoney: La prophylaxie du tétanos.
4. Dr Emile Gaumond: Nouvelles idées sur le syndrome eczéma-prurigo de Besnier.
5. Dr Maurice Beaulieu: Pneumothorax spontané récidivant.
6. Dr Jean-Maurice Blais: L'anatomie clinique et dynamique.

Mardi, 6 juin

1. Dr Rosaire St-Pierre: Incidence et signification des blocs droits incomplets.
2. Drs Claude Brosseau et Léandre Tocantins: L'acide epsilon amino-caproïque agent antifibrinolytique. Etude clinique de son influence sur le saignement post-opératoire consécutif à la prostatectomie.
3. Dr Edmond Laurendeau: Possibilité de troubles d'origine électrolytique dans les lésions infarctoïdes du myocarde.
4. Dr Marc Cantin et Hans Selyé: Rôle de la parathyroïde, de la thyroïde et de la résistance non-spécifique dans les cardiopathies urémiques.
5. Drs Paul David et Yvette Lemire: Résultats de l'anticoagulothérapie à long terme chez le coronarien.
6. Dr Michel Vulpe: Etudes sur l'encéphalite allergique expérimentale.

Symposium: les familles canadiennes françaises et leurs maladies

Animateur: Dr Jean-Louis Bonenfant.

1. Les maladies pédiatiques: Dr Claude Roy.
2. Les maladies sanguines: Dr Jean-Marie Delâge.
3. Les maladies neuro-psychiatriques: Dr Lionel Lemieux.
4. Les maladies métaboliques: Dr Jean-L. Beaudoin.
5. Aspects démographique de la génétique clinique: M. Yves Martin, professeur à la Faculté des Sciences, Université Laval.
6. Principes de méthodologie en génétique clinique: Dr Lévi Chouinard.

Forum: l'athérosclérose

Animateur: Dr Carlton Auger.

1. La physiopathologie de l'athérome: Dr Carlton Auger.
2. Les coronaires: Dr Paul David.
3. Les artères carotides et vertébrales: Dr Claude Bélanger.
4. Les gros vaisseaux: Dr Georges-Etienne Cartier.

5. Les artères rénales: Dr Louis Coulonval.
6. Les vaisseaux périphériques: Dr Edouard Beaudry.

Colloque: les actualités en obstétrique

Animateur: Dr René Simard.

Avec la collaboration de MM. les docteurs: Roger Brault, Marcel Carbotte, François-Xavier Demers, Jean de St-Victor, Prime Duchaîne, Oscar Garant, Guy Gélinas, Vincent Guimond, André-B. Marquis et Grégoire St-Arnaud.

De plus amples informations peuvent être obtenues auprès de Dr Jacques Turcot, Sécretaire, Association des Médecins de Langue Française du Canada, Faculté de Médecine, Université Laval, Québec.

BOOK REVIEWS

CLASSICS OF MEDICINE AND SURGERY. Collected by C. N. B. Camac. 435 pp. Illust. Dover Publications, Inc., New York; McClelland & Stewart, Toronto, 1960. $2.25.

This book was first published in 1909 by the W. B. Saunders Company. The Dover edition, which has the same text as the original, demonstrates the sturdiness, durability, attractiveness and economy of the best type of paper-back publication. At less than half the price of a hard-cover volume, this book is a bargain. Anyone with a few books about medical history will wish to have this one in his bookcase.

The contents consist of original writings of Lister on antisepsis, Auenbrugger on percussion, Laennec on auscultation, Harvey on the circulation, Morton and Simpson on anesthesia, Holmes on puerperal fever, and Jenner on smallpox vaccine. Brief biographies describe the authors and the difficulties which they encountered. The authors were all courageous men who sought truth, not popularity and approval; only one, Morton, appeared to be looking for financial gain. A number of these great doctors predicted accurately that their discoveries would meet serious opposition; several suffered the worse fate of being ignored until a later generation appreciated the validity of their observations. These papers are of great interest to read in their entirety. With a few exceptions the writing is fresh, instructive and entertaining, in striking contrast to modern, terse, emasculated medical prose. What would today's editor do with the personal (but not egotistical) manuscript of Jenner, who takes you with him to the farm houses in his neighbourhood and introduces you to the members of the households?

One cannot resist comparing the worth of the papers on grounds of originality and ability to open up new areas of medical enquiry. Nearly all rank very high. Laennec and, to a lesser extent, Auenbrugger sparked the remarkable interest in methods of physical examination and in clinico-pathological correlations which have been responsible for much of the progress of clinical medicine in the last one hundred and fifty years. With uncanny insight, Jenner, the father of immunization, recognized viruses and showed how to make beneficial use of a harmless organism to prevent the proliferation of one of the great scourges of mankind. Lister made modern surgical progress possible, while Harvey's work is a foundation stone of physiology. The introduction of ether and chloroform as anesthetics, although not the result of long personal experimentation or reasoning, opened up new fields of surgery and relieved human suffering in a way perhaps unequalled by any other discovery. Holmes' paper, in comparison with the others, proves somewhat disappointing. He begins by saying, "In collecting, enforcing and adding to the evidence accumulated upon this most serious subject, I would not be understood to imply that there exists a doubt in the mind of any well informed member of the medical profession as to the fact that puerperal fever is sometimes communicated from one person to another, both directly and indirectly." He goes on to quote from a number of publications (one as early as 1795, nearly fifty years before his paper) which contain observations suggesting the infectious origin of the disease. Holmes' original contribution consisted in a survey not of his own experience, for he had little or no obstetrical practice, but of the observations of doctors in his community. Perhaps it is the brilliant writing of "The Autocrat of the Breakfast Table" which has raised this essay to the exalted company of the medical immortals.

THE SURGICAL TREATMENT OF INTRACRANIAL MENINGIOMAS. Collin S. MacCarty. 69 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1961. $5.00.

The subject matter of this monograph was originally presented to the Congress of Neurological Surgeons, a group composed of some of the younger neurosurgeons in America. The author is well aware of the limitations of such a brief dissertation on the surgery of meningiomas, but is hoping that he might give one or two pointers regarding the successful removal of these tumours. In this he succeeds very well, bringing out the basic principles of the approach and removal as well as discussing some of the calamities that may ensue during the operation and the means to combat these. The monograph devotes one short chapter each to meningiomas at the 12 commonest sites augmenting the text with illustrative cases. The author's S-shaped bilateral incision as an approach to bilateral parasagittal meningiomas is worthy of note, but when dealing with these tumours he does not mention the value of sagittal sinograms in determining patency of the superior longitudinal sinus prior to operation. On the whole his descriptions of individual cases demonstrate sound preoperative and operative procedure, the latter being well illustrated by the artist Russell Drake. No mention is made of the value of radiotherapy following partial removal nor of its value preoperatively to shrink some of the "malignant meningiomas" and make their removal easier. The book will have served its purpose well if it teaches the younger neurosurgeon how satisfactorily these tumours can be dealt with by using the well-tried techniques of one of the more experienced members of the fraternity.

(Continued on page 1220)

widely used...
widely useful...

PRO-BANTHĪNE® *with* DARTAL®

In Emotionally Based Smooth-Muscle Spasm

The wide variation in severity of emotionally based gastrointestinal dysfunctions requires a wide range of therapeutic control. Pro-Banthīne with Dartal combines, in a single tablet, both therapeutic activity and flexibility to relieve the psychic stress and the enteric distress of such dysfunctions.

Clinical trials[1,2] demonstrate that Dartal may be used to treat successfully a wide range of emotional disturbances through simple adjustment of dosage. Similarly, the usual daily dosage of Pro-Banthīne may be doubled or tripled without appreciably increasing the incidence or severity of secondary effects[3] and tablets of plain Pro-Banthīne may be added to the antispasmodic-tranquilizing regimen of Pro-Banthīne with Dartal when profound suppression of gastrointestinal hyperactivity is indicated.

Combination of the outstanding anticholinergic, Pro-Banthīne, with the well-tolerated tranquilizer, Dartal, provides the therapeutic reliability needed in the management of emotionally influenced smooth-muscle spasm.

specific clinical applications: Functional gastrointestinal disturbances, gastritis, pylorospasm, peptic ulcer, spastic colon (irritable bowel), biliary dyskinesia.

dosage: One tablet three times daily.

supply: Aqua-colored, compression-coated tablets containing 15 mg. of Pro-Banthīne (brand of propantheline bromide) and 5 mg. of Dartal (brand of thiopropazate dihydrochloride).

1. Hock, C. W.: Treatment of Gastrointestinal Disorders with an Anticholinergic Tranquilizer Combination, J. M. A. Georgia 48:218 (May) 1959. 2. Investigators' Clinical Reports: Analysis of reports by 117 physicians in 500 patients. 3. Barowsky, H.; Schwartz, S. A., and Lister, J.: Experience with Short-Term Intensive Anticholinergic Therapy of Peptic Ulcer, Am. J. Gastroenterol. 27:156 (Feb.) 1957.

G. D. SEARLE & CO. OF CANADA LTD.
247 QUEEN ST., E., BRAMPTON, ONT.

Canad. M. A. J.
May 27, 1961, vol. 84

(Continued from page 1218)

TEACHING THE EDUCABLE MENTALLY RETARDED. Practical Methods. Malinda Dean Garton. 233 pp. Illust. Charles C Thomas, Springfield, Ill., 1961. $7.50.

This is essentially a practical manual for teachers of the mentally retarded. It includes helpful chapters on the characteristics of the educable mentally retarded, objectives for their education, curriculum suggestions, and methods for carrying out the suggestions. Adequate instructions are given for developing a modified core curriculum which, it is claimed, has proved successful in maintaining interest throughout a series of experiences and activities. Reading, writing, spelling and arithmetic are treated in detail, while brief but informative chapters are devoted to music and art. The advantages of an art program in lessening fears and tensions are recognized, and several pages are devoted to the value of painting and modelling in developing self-confidence. Teacher-parent relationships and the maintenance of discipline are amongst the other topics discussed.

The book is well illustrated and clearly written, and possesses an extensive bibliography. It should prove useful to teachers of the educable mentally retarded.

HENRY STANLEY PLUMMER. Fredrick A. Willius. 70 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $4.50.

This biographical sketch of one of the "architects" of the Mayo Clinic from 1900 until his death in 1939 is written by an associate who is now Emeritus Professor of Medicine of the Mayo Foundation.

Dr. Plummer was outstanding in the medical developments of his time, his main interests being in the treatment of thyroid diseases and in the establishment of radiological diagnosis in the Mayo Clinic. He was equally interested in the physical development of the Clinic and he was responsible for many of the architectural details of the first Clinic building, which was begun in 1912 and completed in 1914. The Mayo Clinic building of 1929 bears his name, partly on account of the many technical innovations he added to it.

This is a very readable little book, both for those who are interested in the history of the Mayo Clinic and for those who are interested in a great and modest personality.

FRENCH'S INDEX OF DIFFERENTIAL DIAGNOSIS. Edited by Arthur H. Douthwaite. 1111 pp. Illust. John Wright & Sons Ltd., Bristol; The Macmillan Company of Canada Limited, Toronto, 1960. $21.50.

This classical text on differential diagnosis has always served as an extremely valuable reference source in this field. The new edition has undergone considerable revision and much of the terminology has been modernized. It continues to be a valuable source of information for graduate trainees, but generally speaking, it is considerably too detailed for undergraduate use, except for preparation of seminars. The photographic illustrations could be revamped and brought up-to-date with more modern photographs. This would greatly improve the general impression that the book gives to the reader.

DISEASE AND THE ADVANCEMENT OF BASIC SCIENCE. Edited by Henry R. Beecher. 416 pp. Illust. S. J. Reginald Saunders and Company Limited, Toronto, 1960. $13.75.

This volume is developed from the Lowell Lectures which were given at Harvard University in 1958. The main purpose of the volume is to establish the validity of the belief that some forms of basic scientific advances can be made only from the study of disease, either organic or functional. Some 21 contributors have had a part in the making of the book and every one of these is known or accepted as an authority in the field about which he has written. Thus readers will find only minor matters for doubt or disagreement.

Even a cursory examination will probably be enough to convince the doubting that there is an intimate and wide relationship between the basic sciences and many of the diseases that may be found in humans and in non-human organisms. The presentations vary somewhat in length, and the clarity is not of a uniform quality, but the approach is comprehensive and few important details are omitted. Some readers will find the histological reviews the most attractive features while others will obtain more comfort and satisfaction in being up-to-date in their attitude to the mangement of conditions that are still not fully a part of medical knowledge. Although this book is not entirely encyclopedic, the information it contains is enough to bring the general practitioner abreast of what is known about the problem that is mystifying him.

The book can be recommended on the whole with frankness. However, there are some drawbacks, the chief of which is the writing style which is sometimes a trifle obscure and nearly always heavy. Most readers will probably find that the work requires not only a certain amount of curiosity but a patient perseverance.

GROUP PROCESSES: Transactions of the Fifth Conference, Princeton, N.J., October 12-15, 1958. Edited by B. Schaffner, Columbia University, New York. 196 pp. Illust. The Josiah Macy, Jr. Foundation, New York, 1960. $4.50.

This book will be of interest to anyone who wishes to study the interchange between a group of very distinguished scientists informally discussing three diverse topics. The group includes representatives of various branches of medicine, sociology, psychology, anthropology and zoology.

The three topics dealt with in the three sessions reported are: "Experimental Aspects of Pediatrics", "The Analysis of Behavior in Terms of Control Systems" and "The Cult as a Condensed Social Process".

The discussions were sponsored by the Josiah Macy, Jr. Foundation for ". . . the promotion of communication, the exchange of ideas and the stimulation of creativity among the participants". As noted on the dust cover, "Every effort is made to preserve the informal nature of the meetings so that the reader may participate vicariously in the give and take of the lively discussions." It is hoped that these conferences and the subsequent publication of an only moderately edited version of what was actually said, will stimulate research and help to ". . . promote effective communication across departmental walls which tend to isolate the professions and specialties from one another".

In the opinion of this reviewer, the book is useful for the purpose for which it was designed. Incidentally, the participants present some very interesting material.

WANTED.—MEDICAL DOCTOR for private practice in rural community in northwest Saskatchewan. New 10-bed hospital with x-ray, laboratory and excellent nursing staff. Population of hospital area, approximately 2000. Fully modern doctor's residence and new office facilities provided without charge. No other doctor in the community. Position available at once. For full particulars apply to Mr. W. F. Kuffert, Chairman, Rabbit Lake Union Hospital, Rabbit Lake, Saskatchewan.

Practices

NOTE: To avoid the publication of misleading information, all advertisers under the classification "Practices" in the Canadian Medical Association Journal should furnish the following information:

Population of community and surrounding territory served.

Number of doctors now practising in the community.

Location of nearest doctor if the community has no resident physician.

Location of nearest hospital.

Description and suggested price of premises for office and residence.

Whether or not an introduction of at least two months' duration may be afforded a prospective purchaser.

OFFICE WITH HOUSE FOR SALE in a large southern Ontario town. Beautiful location. Excellent hospital facilities. Introduction if desired, terms can be arranged. Owner specializing. Reply to Box 770, CMA Journal, 150 St. George St., Toronto 5, Ont.

GENERAL PRACTICE in small town in eastern Ontario available by June 1961. Gross income $20,000 per year. Accredited hospital, 15 miles away over first class roads. Reply to Box 459, CMA Journal, 150 St. George St., Toronto 5, Ont.

FOR SALE.—Established general practice, southern Ontario village. Good income, pleasant living and recreational area. Attractive home and office. Terms to suit purchaser. Small downpayment and low price to facilitate immediate sale. Specializing. Reply to Box 466, CMA Journal, 150 St. George St., Toronto 5, Ont.

GENERAL PRACTICE FOR SALE in Manitoba town of 1500. Very large district. Good highways. 32-bed hospital located in town. One other doctor. For sale—records, office equipment and furniture for $2000. Immediate possession. Please reply to Box 468, CMA Journal, 150 St. George St., Toronto 5, Ont.

WELL-ESTABLISHED, unopposed general practice for sale in eastern Saskatchewan. Gross income over $25,000 from practice and $22,000 from small drug store associated. 16-bed hospital in town, good schools. No real estate to buy. Asking less than 25% of one year's gross to cover equipment and drug stock. Will accept downpayment and terms available on balance. Apply to Box 467, CMA Journal, 150 St. George St., Toronto 5, Ont.

Residencies and Internships

RESIDENT IN RADIOLOGY, first year, wanted for July 1, 1961 or January 1, 1962 for a 480-bed new medical center affiliated with medical school. Stipend $250 first year, $275 second year, $375 third year, per month with room and laundry. For particulars apply to Dr. Julian O. Salik, Sinai Hospital of Baltimore, Inc., Greenspring at Belvedere, Baltimore 15, Maryland, U.S.A.

ROTATING INTERNSHIPS FOR 1961-62 for fully accredited 186-bed hospital with active teaching program. Approved by A.M.A. located near New York city. ECFMG certification required. Stipend—$250 a month, plus room and board. Travel allowance $300. Write, Director of Medical Education, The Griffin Hospital, Derby, Connecticut, U.S.A.

OPENINGS FOR SEVERAL HOUSE OFFICERS in three hospital combined program. Two private hospitals, one brand new charity hospital. Approved one year rotating internship, approved two year general practice residency, several specialty residencies. Stipend $400 for interns, $425 for residents, exclusive of meals or maintenance. Appointment July 1. Apply Director of Medical Education, 609 Brent Annex, or phone HE. 8-8581, Pensacola, Fla., U.S.A.

U.S.A., St. Luke's Hospital, Newburgh, New York. (On Hudson River, 60 miles north of New York City, population 35,000). Rotating internships, approved by the American Medical Association. Very active general hospital, 247 beds (currently expanding to 310 beds). Full educational training program. Stipend $250 per month with full maintenance. E.C.F.M.G. certification required. Apply to Director of Medical Education, St. Luke's Hospital, Newburgh, New York, U.S.A.

RADIOLOGY RESIDENCY AVAILABLE.—708-bed general hospital, midwest. Complete resident training for American board of radiology. Large new department including therapy and isotope divisions. Complete teaching facilities; staffed with board certified radiologists and six residents. Large volume of teaching material and large well organized teaching files, lecture and conference series, university affiliation. Good housing facilities, stipend from $3900 to $5400. Apply to Box 469, CMA Journal, 150 St. George St., Toronto 5, Ont.

MEDICAL NEWS *in Brief*

(Continued from page 1209)

CANADIAN CANCER SOCIETY

The Annual Meeting of the Canadian Cancer Society will be held in the Charlottetown Hotel, Charlottetown, Prince Edward Island, on Thursday, June 15, 1961, at 8.00 p.m. (local time) to receive reports of the Directors and Auditors, and to transact such other business as may properly be brought before the meeting.

—

RUSSIAN SYMPOSIUM ON CARDIOTHORACIC SURGERY

The January 1961 issue of the Russian journal, *Khirurgiia*, is devoted to a symposium on cardiothoracic surgery. An article by Sven of the University of Colorado, U.S.A., discusses the application of hypothermia and extracorporeal circulation to vascular surgery. Gadzhiev directs attention to the anomalies of the pulmonary arteries which may be encountered at operations on the lungs, and reports two cases of intralobar sequestration. Diagnostic studies of pressure in the left auricle by means of transbronchial puncture are described by Belobradek, Petrle and Prokhazka. Astrakhantseva and Saveliev discuss the complications associated with puncture of the left auricle and catheterization of the left heart. Electrostimulation of the heart by means of a pacemaker is described by Bredikis, and Izbinsky discusses the role of tracheostomy in the prevention and treatment of postoperative respiratory complications following chest surgery. The source of bleeding, management and definitive treatment of hemoptysis as encountered in 86 patients is reported by Neimark.

—

CATHOLIC HOSPITAL ASSOCIATION OF THE U.S.A. AND CANADA, 46th ANNUAL CONVENTION

The Catholic Hospital Association of the U.S.A. and Canada will hold its 46th annual convention in Cobo Hall, Detroit, Mich., June 12-15. The theme this year will be "Attitudes, Action, Achievement". Approximately 5000 religious and lay personnel from hospitals throughout the U.S.A. and Canada are expected to attend.

THIRD INTERNATIONAL CONVENTION OF X-RAY TECHNICIANS

The Third International Convention of X-Ray Technicians, sponsored jointly by the American Society of X-Ray Technicians and the Canadian Society of Radiological Technicians, will be held in the Queen Elizabeth Hotel, Montreal, June 24 to 29, 1961.

The joint committees under the general chairmanship of Mr. G. Archie Wilkinson, R.T., Supervisor of the Department of Radiology of the Royal Victoria Hospital, Montreal, have prepared an attractive program of lectures, luncheons and entertainment. Refresher courses will be held daily. Distinguished speakers will address the scientific sessions and two memorial lectures will be given, the Jerman Memorial Lecture presented by the A.S.X.T. and the Welch Memorial Lecture arranged by the C.S.R.T.

An invitation is extended to all technicians and radiologists to attend.

FURTHER STUDIES ON THE RATIO TOTAL SERUM CHOLESTEROL/(PER CENT ALPHA LIPOPROTEINS)^2

Determination of the percentage of alpha lipoprotein in human serum has been considered an aid in the biochemical diagnosis of coronary artery disease (*Canad. M. A. J.*, 83: 76, 1960). Further appraisal of this approach on a large scale necessitated a more rapid and accurate method of lipoprotein analysis. At the Montreal Physiological Society Meeting, December 1, 1960, Allard and Choquette described a new electrophoretic procedure and its application in the study of a series of coronary and non-coronary subjects. The method consists essentially in straining the serum with an alcoholic solution of acetylated sudan black B prior to electrophoresis for 16 hours in a Durrum-type system, using Whatman 3 MM paper. The papers are then dried at 100° C. for 15 minutes and scanned at 500 μ in a calibrated recording densitometer equipped with an automatic integrator. Three peaks are registered. Their surfaces serve in the calculation of the relative proportion of alpha lipoprotein. Application of this procedure in conjunction with total cholesterol determinations confirmed the fact that a value of 0.8 for the ratio total cholesterol/(per cent alpha lipoprotein)^2 sharply segregates coronary from non-coronary subjects. This value enabled the researchers to distinguish 93.8% of the patients with coronary artery disease and 97.8% of the healthy subjects.

CANCER AND AIR POLLUTION

In the last decade, an increasing number of polynuclear aromatic hydrocarbons, some of them of proven potency as animal carcinogens, have been identified in the urban atmosphere and in the exhaust gases of gasoline and diesel engines. Other carcinogens are present in coal tar, asphalt, bituminous coal and petroleum products, isopropyl oil, effluents of industrial and domestic furnaces and in dust from rubber tires and asphalted and oiled roads. There are also known occupational, respiratory carcinogenic agents associated with industries involving arsenicals, asbestos, chromite, radioactive dust and gases, tar distillation, and many others. It has been estimated that about 16 mg. of 3,4-benzpyrene may be inhaled and retained in the lungs from urban air pollution during a life-time. This quantity represents a dose approximately 40,000 times greater than that capable of producing cancer in mice by subcutaneous introduction (0.4 μg.). Since the benzpyrene content of urban air may be increased four-fold during smoggy days and this compound is only one of an increasing number of carcinogenic compounds isolated from atmospheric pollution, the actual total of such substances accumulated in the lungs would be very much greater. According to Hueper, the much greater incidence of lung cancer in males than in females may be due to the relatively greater number of males employed in occupational activities, both indoor and outdoor, involving exposure to contaminated industrial or urban atmospheres. Males predominate in tasks that require heavy physical labour, in motor and other transportation activities, in iron and steel, mining and smelting and other heavy-industry occupations

(Continued on page 30)

MEDICAL NEWS *in brief*

(Continued from page 29)

where exposure to carcinogenic pollutants is greater. Females, on the other hand, spend a larger portion of their lives in the cleaner air of suburban communities.—M. Katz, *Occupational Health Review*, Vol. 13, No. 1, 1961.

ELEANOR ROOSEVELT CANCER FELLOWSHIPS

The International Union Against Cancer, through funds made available by the Eleanor Roosevelt Cancer Foundation, will award annually fellowships for research on cancer. These fellowships have been created in the belief that the international exchange of scientists between centres with kindred interests will facilitate the sharing of knowledge and thereby contribute to the control of cancer.

These are senior postdoctoral awards designed for the support of persons who, as full-time members of the staff of universities, teaching hospitals, research laboratories or other institutions, have demonstrated interest and outstanding ability or promise as independent investigators in the field of research on basic cancer, its experimental and clinical aspects, and who wish to broaden their experience by a period of study in another country. The duration of the fellowships ordinarily will be one year but this period may be extended or shortened in special circumstances. The stipend will be based on the current salary of the applicant and the salary of persons of comparable qualifications in the place where the applicant expects to study. An allowance will be made for dependents and for costs of travel to and from the fellow's residence and the institution where he will work.

Application forms and additional information may be obtained from the International Union Against Cancer, P.O. Box 400, Geneva 2, Switzerland.

Grâce aux fonds mis à sa disposition par la Fondation Eleanor Roosevelt contre le cancer, l'Union Internationale contre le Cancer distribuera chaque année des bourses pour les recherches sur le cancer, bourses créées dans l'idée que les échanges internationaux de travailleurs scientifiques entre centres à intérêts apparentés faciliteront la diffusion des connaissances et contribueront ainsi à venir à bout du cancer.

Il s'agit de stipendiums accordés à des universitaires ayant fait leur doctorat et qui—travaillant à plein temps dans les universités, hôpitaux universitaires, laboratoires de recherches ou autres institutions, ayant fait preuve d'intéret et de capacités spéciales, ou en bonne voie de devenir des chercheurs indépendants dans le domaine des travaux sur le cancer lui-même et sur ses aspects expérimentaux et cliniques — désirent élargir leurs connaissances par une période d'étude dans un autre pays.

La durée normale de la bourse accordée sera de un an, mais cette période peut être prolongée ou abrégée dans certaines circonstances particulières. Le montant sera calculé d'après le salaire normal de l'intéressé et celui des personnes ayant des qualifications comparables au lieu où il désire étudier; une allocation est prévue pour les personnes à sa charge, ainsi que pour les frais de voyage (aller et retour) du domicile à la nouvelle place.

JOINT MEETING OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS AND AMERICAN MEDICAL ASSOCIATION

The 27th Annual Meeting of the American College of Chest Physicians will be held at the Commodore Hotel, New York City, Thursday, June 22, to Monday, June 26. Scientific sessions will open on Saturday, June 24, and will end on Monday, June 26.

A joint session with the Section on Diseases of the Chest of the American Medical Association will be held at the Coliseum on Monday, June 26. This will be the first joint meeting in the history of the two societies.

The popular Fireside Conferences, also to be joint sessions sponsored by both the A.M.A. and the College, will be held at the Commodore Hotel on Monday evening, June 26.

THE CANADIAN MENTAL HEALTH RESEARCH FUND

The national president of the Canadian Mental Health Association, J. S. D. Tory, Q.C., has announced that Dr. Ray F. Farquharson will be honorary director of the Association's research fund.

The fund, financed by voluntary donations to mental health campaigns, was established by the Association to ensure continuing research in mental health and illness. Single grants up to $25,000 are awarded to encourage scientists to make a career of mental health research. These are among the largest scientific grants now offered in Canada.

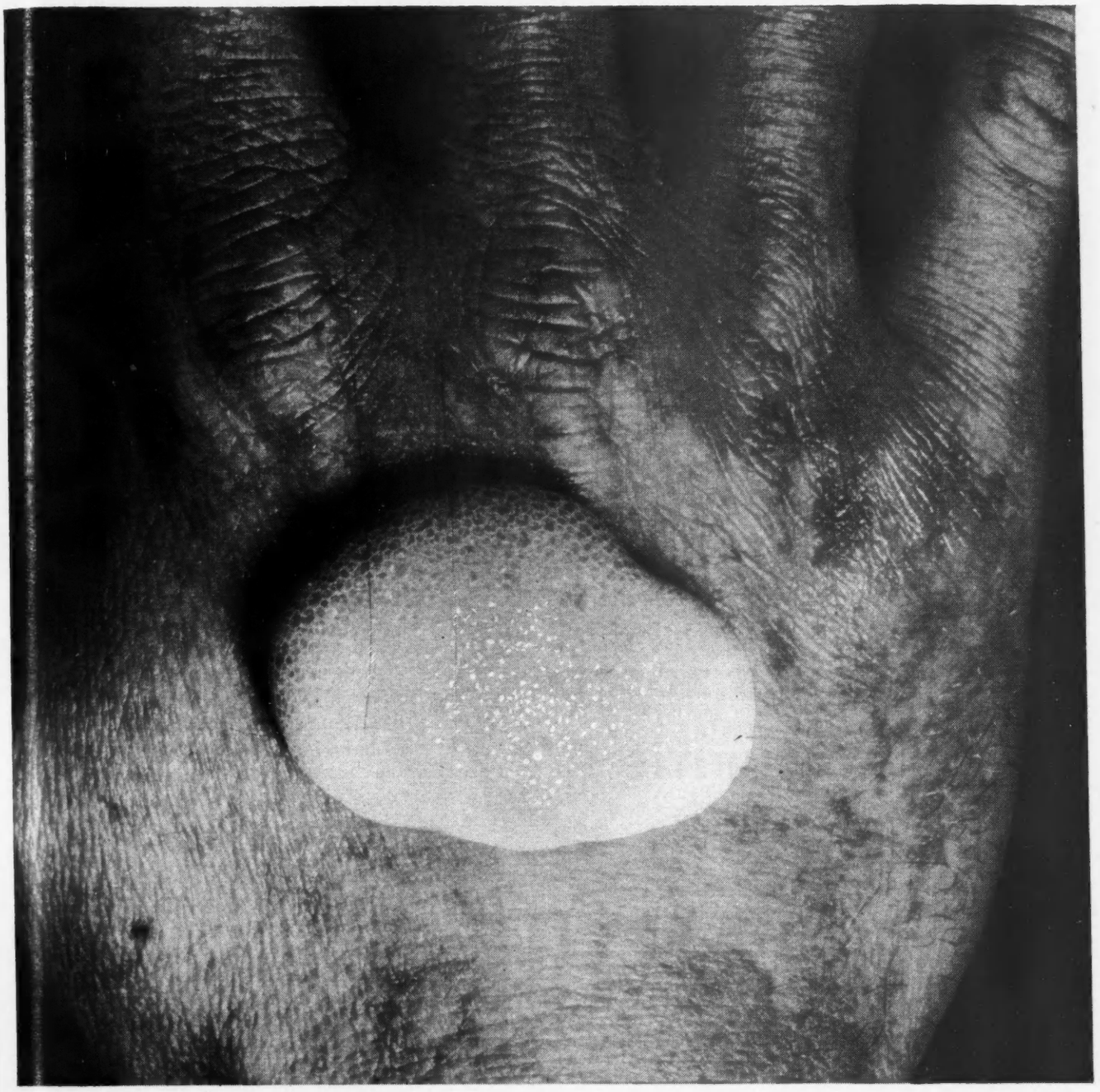
Dr. Farquharson, Emeritus Professor of Medicine of the University of Toronto, is also chairman of the Medical Research Council of Canada which was created last November. He has been physician-in-chief at the Toronto

Ashley & Crippen

Dr. R. F. Farquharson

General Hospital, president of the Royal College of Physicians and Surgeons of Canada, and a member of the Defence Research Board. He is a member of the board of governors of York University.

(Continued on page 32)



Neo-Aristoderm® Foam

Neomycin-Triamcinolone Acetonide Lederle

SPREADS MORE EASILY AND EVENLY THAN OINTMENT

Your patients will appreciate the ease of application to tender lesions, and the lack of greasiness which makes NEO-ARISTODERM FOAM cosmetically superior to other topical formulations. The pressurized dispenser delivers foam directly to the site of inflammation helping to eliminate waste. NEO-ARISTODERM FOAM contains triamcinolone acetonide which has ten times the potency of topical hydrocortisone, combined with neomycin to offset secondary infection.

Lederle CYANAMID OF CANADA LIMITED *Montreal*

MEDICAL NEWS *in brief*
(Continued from page 30)

Two Canadian scientists are at present working on studies supported by C.M.H.A. research fund awards. They are Dr. Noël Mailloux of the University of Montreal and Dr. Patrick McGeer of the University of British Columbia.

—

DEVICE AIDS SURGERY OF PARKINSONISM

A new technique that gives a neurosurgeon objective moment-by-moment information on how surgical procedure affects the tremor of the parkinsonism patient on whom he is operating was described to the Chicago Neurological Society by three Northwestern University physicians and an electronics engineer. The technique, making use of an instrument originally developed for testing aerodynamic surface vibrations in aircraft wings and guided missiles, was reported by Dr. Joel Brumlik, director of Northwestern's laboratories for parkinsonism research in neurology and psychiatry; Dr. Nicholas Wetzel, Assistant Professor of Surgery; Dr. Benjamin Boshes, Professor of Neurology and Psychiatry and chairman of the department; and Mathew Petrowick, the engineer who designed the instrumentation techniques.

Preliminary results in four patients indicate that the monitoring device showed a dramatic reduction in tremor when the surgical lesion is produced. The monitor consists of a device that can measure a tremor of 0.03 mm. The device may be taped to any part of the body and sends the signal on the amount of tremor through a detector-amplifier to a direct-writing oscillograph that produces a graphic tracing of tremor shape, amplitude and frequency. The sensing device, called an accelerometer, is small, easily applied, and does not interfere with the surgical procedure.

While cautioning that their report was a preliminary one, they said that the results indicate the great potential of such a method. If the data collected during operations are correlated with patient improvement, a pattern may evolve, indicating and defining the location or locations of choice for such surgery.—*Medical Tribune.*

—

CANADIAN ASSOCIATION OF PHYSICAL MEDICINE AND REHABILITATION

The Canadian Association of Physical Medicine and Rehabilitation will hold its Ninth Annual Meeting on Thursday, Friday and Saturday, August 24-26, 1961, in the Bessborough Hotel, Saskatoon, Sask. The scientific sessions will take place on Thursday and Friday in the auditorium of the University Hospital, Saskatoon.

All physicians interested in physical medicine and rehabilitation are welcome to attend this conference. Enquiries should be addressed to Dr. Maurice Mongeau, Secretary, Canadian Association of Physical Medicine and Rehabilitation, 6265 Hudson Road, Montreal 26, Que.

—

DR. F. R. ECCLES MEMORIAL MEDICAL ALUMNI LECTURESHIP

The twenty-first Dr. F. R. Eccles Memorial lectureship, which is held annually at the University of Western Ontario, will be presented this year on Wednesday, October 11. The guest lecturer will be Dr. Harold G. Wolff, Professor of Medicine, Cornell University. Further details of the program for this occasion will appear in a subsequent issue of the Journal.